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THE PROBLEM OF PREMATURITY*

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IN ORDER to bring to light the problems associated with it, the prematurity situation was studied in one hospital in Halifax, Nova Scotia, between the years 1948 and 1958 inclusive. Of 25,509 babies born in this hospital during this period 783 were premature, i.e. they weighed more than 500 g. but less than 2500 g. The incidence of prematurity was 3.06%. This low figure prompted an enquiry at the only other obstetrical hospital in the city. In the 10 years noted above, they had 732 prematures in 28,862 deliveries, an incidence of 2.54%. These low figures are significant when we realize that: (1) 99% of the women in this city are delivered at these two hospitals, and (2) the average incidence reported generally in the Western world is around 7% as seen in Table I.

TABLE I.

	Incidence
Canadian average	7%
Ontario average	6.8%
Nova Scotian average	5.9%
American average	7.4%
Edinburgh average	7%
Halifax average	3.06% 2.54%

During the same 10-year period, there were 477 stillbirths and 400 neonatal deaths, giving a total of 877 perinatal deaths in hospital No. 1. Of these, 221 were associated with premature delivery. This means that although prematurity occurred in only 3.06% of instances, it accounted for over 28.2% of the perinatal death rate. This fact in itself is enough to warrant a serious study of prematurity. The same situation prevails in other countries—as evidenced by Table II, showing that although the incidence of prematurity is low, it accounts for one-quarter to one-half of all perinatal deaths in these countries.

As noted above, 783 premature babies were born in the 10 years studied. Of these we can assign a definite maternal factor related to prematurity in but 311 cases or approximately 39.7%. Conversely,

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TABLE II.

Place	*Incidence*	*Percentage of perinatal death rate*
Halifax—hospital No. 1	3.06%	28%
—hospital No. 2	2.54%	
U.S.A. (national study)	7.4%	66%
England and Wales (annual report, 1954)	7%	28%
Edinburgh	7%	

no specific maternal factor could be demonstrated in 472 cases, or approximately 60.3% of the study series. This is much the same finding the world over—there is no known cause or related factor in over one-half of the cases.

TABLE III.—MATERNAL FACTORS IN PREMATURE LOSS

	No. of cases	*Percentage of maternal factors*	*Percentage of total*
Toxæmia of pregnancy	79	25.4%	10%
Antepartum hæmorrhage	145	46.7%	18.6%
Multiple pregnancies	57	18.3%	6.5%
Elective Cæsarean section	9	2.8%	1.01%
Medical and gynæcological complications	12	3.8%	1.3%
Congenital abnormalities	9	3.0%	1.03%
	311	100%	39.7%

In the cases listed above, all factors were included which might conceivably be related to the prematurity. Many of them probably played no part, yet because they are associated they must be included.

From a review of the histories of patients who delivered full-term babies, approximately 23% of their previous pregnancies were found to have terminated in prematurity or abortion. In the premature group, however, there is twice the incidence of previous abortion and prematurity. Does this

TABLE IV.—HISTORY OF PREVIOUS ABORTION OR PREMATURITY

	History of abortion	*History of prematurity*	*Total*
Full term	12.5%	11%	23.5%
Premature	22.3%	24.3%	46.6%

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mean that abortion and prematurity may be one and the same entity and due to one and the same cause? We believe that it does.

For several years a multidisciplinary group from our university have been studying the etiology of abortion.[1] I will not go into detail about this study but would like to summarize our findings and then compare them with a similar study of prematurity.

Early in our investigation the pathologist in our group began to describe proliferative lesions in the villi of aborting placentæ, which he took to be collagen, similar to those found in the tissues of persons suffering from rheumatoid arthritis.[2, 3] These lesions were identified by differential stain and found to exist in the placentæ of over 70% of our abortions. We became quite interested and argued that if he proposed to call abortion a collagen disease, he must prove it. It is well known that in the blood of persons suffering from collagen diseases there is a substance which will agglutinate the red blood cells of sheep. If our assumption that abortion was a collagen disease was correct, then the sera of aborting women should also agglutinate the red blood cells of sheep. To our amazement this did happen—in approximately 70% of cases.[4] We began thinking then of our abortion problem as one with collagen disease. Our psychiatrist became interested and suggested that since some psychiatrists think that the collagen diseases might be psychosomatic in nature, abortion also might be a psychosomatic disease.

TABLE V.—HABITUAL ABORTERS

	No.	*Viable babies*
Long-term study	22	20 (91%)
Short-term study	18	5 (27.7%)

The following study was then instituted. All true habitual aborters admitted to our ward were thoroughly investigated for two days. This investigation included physical examination, pelvic examination, collection of urine for hormonal assay, blood for blood work, and psychiatric and psychological investigation. After this investigation they were sent back to their family doctors. One-half of them were not seen again, but the result of their pregnancies was obtained from their doctor. The other half were followed up with weekly interviews by the psychiatrist. No intentional treatment was given to either of these groups. Table V shows that of those patients who were followed up closely and consequently received psychotherapy inadvertently, only two lost their babies, compared with the short-term studies in which there was about 75% loss. The only difference in these two groups was the psychotherapy given by the close attention they received. These results are significant and would seem to agree with the statements of many authorities today that emotions do play a large part in spontaneous abortion.

TABLE VI.

No.	*Weight of baby*	*Pathology*	*Serology (maternal)*	*Maternal factor*
1	2250 g.	Positive	Positive	Abruptio
2	2250 "	Positive	Positive	Toxic
3	1800 "	Positive	Positive	Toxic
4	2000 "	Positive	Positive	
5	2250 "	Positive	Positive	
6	1700 "	Positive	Positive	
7	1500 "	Positive	Positive	
8	1600 "	Positive	Positive	
9	1500 "	Positive	Positive	
10	1550 "	Positive	Positive	
11	910 "	Positive	Positive	
12	2050 "	Positive	Positive	
13	2200 "	Positive	Positive	
14	900 "	Positive	Positive	
15	900 "	Positive	Positive	
16	1350 "	Positive	Positive	
17	1200 "	Positive	Positive	
18	2000 "	Positive	Positive	
19	1700 "	Positive	Positive	
20	2050 "	Positive	Positive	
21	2200 "	Positive	Positive	
22	1800 "	Positive	Positive	
23	1365 "	Positive	Positive	
24	2000 "	Positive	Positive	
25	1500 "	Positive	Positive	
26	2650 "	Positive	Positive	
27	2250 "	Positive	Positive	
28	1575 "	Positive	Positive	
29	1600 "	Positive	Positive	
30	2000 "	Negative	Negative	
31	2000 "	Negative	Negative	
32	2000 "	Negative	Negative	
33	1950 "	Negative	Negative	
34	2250 "	Negative	Negative	
35	2050 "	Negative	Negative	
36	1650 "	Negative	Negative	
37	1600 "	Negative	Negative	
38	1625 "	Negative	Negative	
39	1700 and 2000 g.	Negative	Positive	
40	2250 g.	Negative	Positive	
41	1600 g.	Negative	Positive	
42	2050 and 2255 g.	?	Positive	
43	1350 g.	Positive	Negative	

What of prematurity? Our findings here have been much the same as in abortion. The placenta shows lesions similar to those found in abortion—the serum contains a substance which will agglutinate the red blood cells of sheep. Is it also a psychosomatic disease? More and more obstetricians are beginning to feel that there are emotional factors associated with the causation of premature loss.

Table VI gives the results of 43 cases of prematurity where the placentæ were investigated for the presence of proliferative lesions and the serum was checked for the presence of an agglutinating factor. The placenta, with differential staining, showed proliferative lesions similar to those found in abortion, and the serum of the mother when typed against the red blood cells of sheep caused them to agglutinate. We see from Table VII that

TABLE VII.—PREMATURITY

Number	*Pathology*	*Serology*
29	Positive	Positive
1	Positive	Negative
1	?	Negative
3	Negative	Positive
9	Negative	Negative

of the 43 cases studied, 29 had positive proliferative lesions in the placentæ and the corresponding sera contained the agglutinating factor. Nine cases had normal pathological findings and normal serology, and four cases showed positive serological but negative pathological findings. One case had positive lesions in the placenta but the serum failed to reveal any agglutinating factor. These lesions are similar to those found in abortion.

Just what do these findings mean? We would suggest that in some way they are the response of the pregnant woman to stress. At the moment we are trying to correlate all our findings, including those from adrenal hormone studies, with the psychiatric factors. Our results would suggest that there is such a correlation and that in time we will be able to show that prematurity like abortion is a psychosomatic disease or, at least, is due to emotional causes. The further we proceed with our study, the more we are persuaded that this is the case.

This study was supported by a Federal Health Grant in collaboration with the project group "combined study of the causes of abortion".

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RÉSUMÉ

Une étude entreprise sur la prématurité dans un hôpital d'Halifax entre 1948 et 1958 en a montré 780 cas sur 25,509 naissances donnant une fréquence de 3.06%. Ce taux est tout de même considérablement inférieur à celui du Canada (7%) ou même de la Nouvelle-Ecosse (5.9%). A cause du taux élevé de mortinatalité ou de mortalité néonatale qui en dépend, la prématurité est responsable de 28.2% des morts périnatales. Dans 37.9% des cas on put identifier un facteur maternel comme la toxémie de la grossesse, l'hémorragie antepartum, les grossesses multiples, les césariennes électives, les complications médicales ou gynécologiques et les anomalies congénitales. Cependant il se peut que certaines de ces causes ne soient qu'associées à la prématurité sans nécessairement y contribuer.

Il est possible que l'avortement et la prématurité ne soient que deux aspects de la même entité et relèvent d'une cause commune. La découverte de lésions prolifératives dans les villosités du placenta dans les cas d'avortement évoque une certaine relation avec la polyarthrite chronique puisque ces lésions sont composées de substance ressemblant au collagène. Partant de cette hypothèse, les auteurs ont recherché le taux d'agglutination des globules sensibilisés chez ces femmes. Une corrélation remarquable de résultats positifs fut découverte. Un psychiatre prit le fil de ces recherches et suggéra que la polyarthrite chronique évolutive ayant des implications psychosomatiques, l'avortement pourrait en avoir autant. On institua de la psychothérapie chez un groupe de patientes ayant des antécédents d'avortements répétés, avec succès. Les données recueillies au sujet de la prématurité sont sensiblement les mêmes que celles que fournit l'avortement. En guise d'explication, l'auteur offre la suggestion que ces lésions sont probablement imputables à la tension et à l'aggression auxquelles certaines femmes enceintes sont sujettes.

CLINICAL, ETIOLOGICAL, AND ECONOMIC ASPECTS OF SALPINGITIS

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SALPINGITIS is a continuing public health problem in many large cities. Receiving Hospital, which is available to the medically indigent of Detroit, had 392 gynæcological admissions in 1958 primarily due to tubal inflammation. This represented 24% of all admissions to the gynæcology service. The 392 cases could be classified as (a) acute and (b) quiescent or interval cases. The average stay for acute cases was 19.9 days and for interval cases 17.8 days. Since only patients severely ill are kept in hospital, there were an estimated 5 to 10 times this number treated as outpatients. Thus, salpingitis is a problem of considerable magnitude.

Investigations into the epidemiological and etiological aspects of this disease have been rather sparse. Most authorities on the subject have been willing to accept the intracellular diplococcus, discovered 80 years ago by Dr. Albert Neisser, as responsible for the majority of cases, or at least the initial episode. If this were true, and with mating urges being what they are, it would perhaps be wishful thinking to expect that many cases could be prevented. It is the purpose of this paper to suggest that a pessimistic attitude toward improvement of the salpingitis situation is unjustified.

K. S. Richardson[1] of Sydney, Australia, in a recent valuable review has reiterated the accepted possible paths of infection in salpingitis. These are:

1. Blood-borne—the classic example of this is tuberculous salpingitis.

2. Spread from adjacent intra-abdominal organs, e.g. an inflamed appendix.

3. Ascending infection—with the bacteria, going salmon-like, retrograde up the menstrual stream and out into the tubes to spawn.

4. Lymphatic spread from the cervix, or "pelvic tonsil", as it has been called, out through the perituterine tissues to the tubes.

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The first two routes are rare in our population, and the last pathway is even rarer. The almost routine inspection of the postpartum cervix and the prompt repair of any cervico-vaginal lacerations have virtually eliminated puerperal parametritis. Falk[2] has demonstrated neatly the importance of the third method of spread. He has performed 1000 cornual resections for chronic recurrent salpingitis and has left the tubes *in situ*. In no case has exacerbation occurred when the mucosal continuity was broken in this manner. This work would also seem to refute the old theory that the organisms can lie dormant in the tubal wall and cause a "flare-up" from time to time (Studdiford[3]).

Recently it was suggested by Nassberg, McKay and Hertig[4] that a physiological salpingitis exists around the time of the menses. Presumably this would help explain the recognized increased frequency of acute salpingitis at this time. Smith and Greene,[5] however, were unable to find changes of similar magnitude and suggested that the described phenomena may reflect the slight trauma of the preoperative pelvic examination. Concerning the clinical observation that salpingitis occurs more commonly at the time of the menses, Hedberg and Spetz[6] in their recent report state that 68% of cases of gonococcal salpingitis and 38% of cases of septic non-specific salpingitis occurred in association with the menses.

The rarity of salpingitis in *normal* pregnancy and the menopause supports the concept that the cervix has a bacteria-repelling role which discourages upward surface spread at times other than the menses.

METHODS OF INVESTIGATION

In this present study, a retrospective survey of 78 consecutive cases of salpingitis plus a prospective analysis of 22 cases was undertaken. In the prospective series, the usual history was supplemented by questions pertaining to personal hygiene, housing facilities and other matters to be discussed later. A complete physical examination was performed on admission and the usual laboratory procedures of hæmoglobin determination, white blood cell and differential count, urinalysis, serology and sedimentation rate were carried out. In addition, in each case before institution of therapy, we obtained: (1) an endometrial biopsy, (2) a Papanicolaou smear of vagina and cervix, (3) a blood culture, and (4) a cervical culture. Whenever a mass was noted in the cul-de-sac, culdocentesis was performed and any pus secured was cultured.

The endometrial biopsies were fixed in formalin. The smears received the usual Papanicolaou staining after fixation. The blood samples (averaging 10 c.c.) were placed in tryptose phosphate broth. Cervical cultures were initially placed in tryptose phosphate broth and then placed in cooked meat media and on the special chocolate agar for the culture of the gonococcus. The next day, aliquots of the cooked meat media culture were plated out on blood agar with phenyl ethanol to inhibit growth of Gram-negative organisms. Also aliquots were added to blood agar with eosin-methylene blue to inhibit Gram-positive organisms. For the anaerobic bacteria, some of the cooked meat culture was plated out on a special blood agar plate and incubated for two days in a hydrogen jar.

Some of the above-mentioned tests were available in the retrospective series, and these will be reviewed also. Of the 78 retrospective cases, 60 were acute and 18 were interval. In the prospective series 19 were acute and three were interval. By and large, the acute cases were severe enough to require hospital admission because of pelvic peritonitis and general toxicity. The interval cases were all admitted because of previous prolonged morbidity or residual masses large enough to require exploratory laparotomy and definitive surgery. In the 79 acute and 21 interval cases, the age distribution is portrayed in Fig. 1.

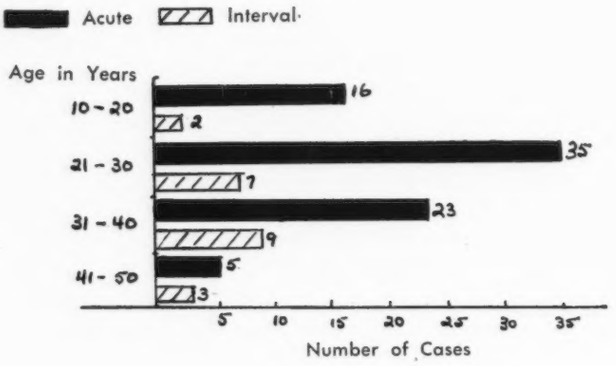

Fig. 1

The racial breakdown (Fig. 2) reflects a preponderance of coloured patients.

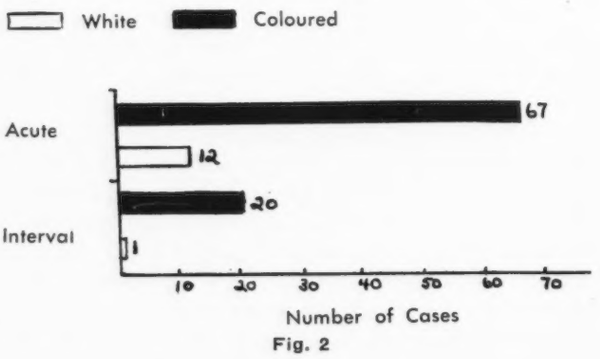

Fig. 2

Parity and abortion rates are interesting and suggest that the frequency of abortion in this economic class is much higher than the classical 10%. Combined figures for the acute and interval cases are presented, since the distribution curve is the same in both groups. No data were available in four of the 100 cases. The total live births in the entire group were 229. The total abortions were 78, for a pregnancy wastage of 34% (Fig. 3).

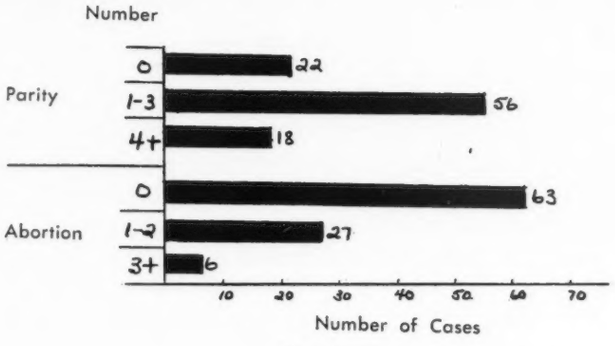

Fig. 3

Whether pregnancy is possible after salpingitis must certainly depend on whether or not the tubes are patent. Moreover, the tubes should not be bound down, or show scarring, thickening or rigidity of the wall. Factors that promote such drawbacks, as pointed out by Hedberg and Spetz, are severe infection and prolonged illness prior to therapy. The person with mild disease who seeks and obtains definitive antibiotic treatment promptly is more likely to remain fertile.

Information concerning the time of last coitus in relation to the start of symptoms was available in 21 cases, and is given in Fig. 4. While the numbers are small, they suggest that coitus has some relation to the start of symptoms in a little over half the cases. Whether a specific infective agent is involved or the trauma of the act itself is causative can only be speculated upon. In 1909, Simpson laid down four conditions to be observed before a case of pelvic inflammatory disease was operable. These are: (1) normal temperature for two weeks, (2) normal white blood count, (3) erythrocyte sedimentation rate of less than 36 mm. in one hour, and (4) no rise in the above after pelvic examination. It is possible that coitus acts like a pelvic examination and promotes spread of a poorly localized infection.

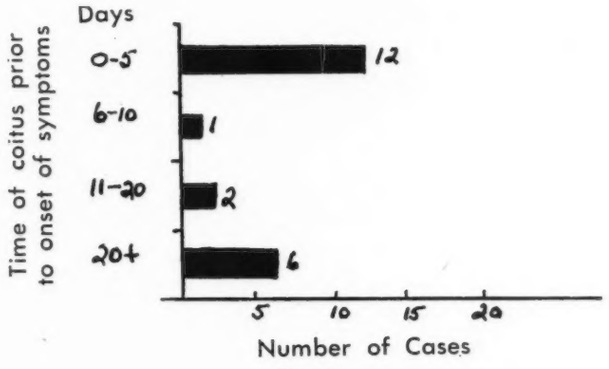

Fig. 4

A positive past history of pelvic inflammatory disease was recorded in 36 cases. A negative history was found in 21 cases, and no information was available in 22.

The day of the cycle on which symptoms began was available in 66 of 79 acute cases and is presented in Fig. 5. The distribution argues against a specific infective agent and suggests that at times in the cycle when the anabolic influence of œstrogen is maximal, the genital tract is less susceptible to infection. We[7] have recently observed the marked beneficial effect of œstrogen on the histological picture in postpartum endometritis.

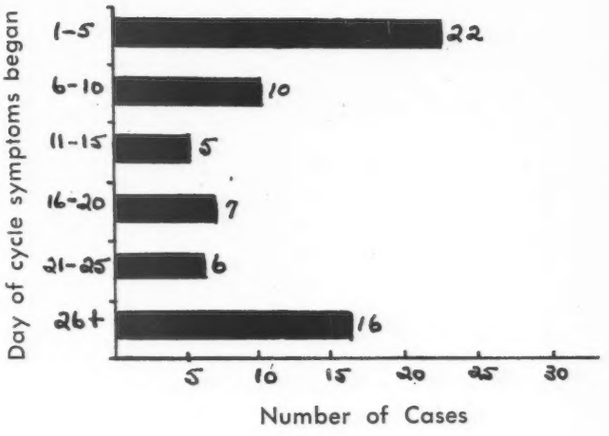

Fig. 5

In the prospective series of 22 cases, inquiry revealed that all but two patients entertained various superstitions concerning their menses, which prevented bathing. Many would not even put a foot in water lest a "severe hæmorrhage" or "arthritis" or "something serious" might occur. These superstitions had been handed down from their ancestors and were believed implicitly. Many of the patients, being poor, lived in flats that shared bathing and toilet facilities with two or three other families. Furthermore, over two-thirds of these women stroked the tissue in an anterior direction from anus to vaginal vestibule, when cleansing themselves following defecation. They had never been instructed otherwise. All of these factors favour a good flora of bowel organisms in the vagina.

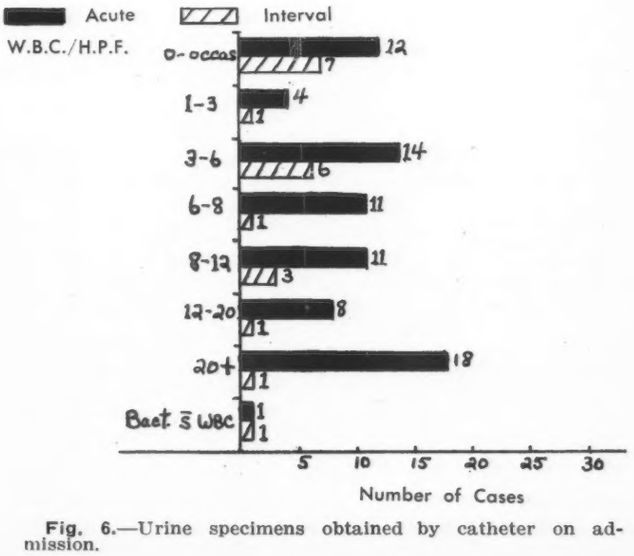

Fig. 6.—Urine specimens obtained by catheter on admission.

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TABLE I.

Cultures	Prospective series			Retrospective series			Totals
	cervix	blood	cul-de-sac	cervix	blood	cul-de-sac	
1. *Staph. albus*, coag. neg.	10	1	1	8		4	24
2. *E. coli*	6			7		6	19
3. Anærobic micrococcus	5			6		4	15
4. γ streptococcus	6		1	4		2	13
5. Bacteroids	3			3		7	13
6. *B. streptococcus*	3		1	4		1	9
7. Diphtheroids	1			1		6	8
8. Aerobic spore-formers	2			5			7
9. White nonhæmolytic micrococcus	1		1	3		1	6
10. *Aerobacter aerogenes*	2			3			5
11. Anaerobic streptococcus				2		2	4
12. *Bac. subtilis*	3			1			4
13. Micro-aerophilic streptococcus	1		1			2	4
14. Pseudomonas	2		1				3
15. Paracolon	1					1	2
16. α streptococcus	1			1			2
17. Nonhæmolytic staphylococcus	1			1			2
18. Microaerophilic micrococcus				1		1	2
19. *Alkaligenes fæcalis*				1		1	2
20. Proteus				2			2
21. Nonhæmolytic streptococcus						1	1
22. *Cl. welchii*				1			1
23. *B. melaninogenicus*				1			1
24. *Cl. perfringens*						1	1
Totals	48	1	6	55	0	40	150

The clinical picture in acute salpingitis of abdominal pain plus systemic signs of infection is well known. Pelvic examination demonstrated adnexal tenderness in all 79 acute cases, masses also being present in 55. The white blood count and sedimentation rate were commonly elevated. Serology was negative in 30, positive in six and not determined in 43 cases. The hæmoglobin level on admission was less than 10 g. % in 25 of 79 cases.

The admission urinalysis reports (specimens obtained by catheter) were interesting. In the great majority of acute cases, a significant degree of pyuria existed (Fig. 6). To a lesser extent the interval cases also manifested this tendency.

Our urology colleagues say that when they see a woman with pyelitis, one of the first things they ascertain is which way she uses the tissue following defecation and very frequently it is in an anterior direction. If this inoculation of bowel organisms can occur in sufficient numbers to produce infection in the anterior pelvic tract, why not in the middle pelvic tract too? Urine cultures were available in several cases and demonstrated the following organisms:

(1) *Staphylococcus albus*	2 cases
(2) γ streptococcus	2 "
(3) *E. coli*	2 "
(4) Diphtheroids	1 case
(5) Paracolon	1 "
(6) *Aerobacter aerogenes*	1 "
(7) *Staphylococcus aureus*	1 "
(8) Gram-positive aerobic spore-formers	1 "

All of the above may be readily found in fæces.

Blood cultures were uniformly unproductive, although taken at the height of fever. Ten c.c. of blood was placed in 90 c.c. of culture medium. Only one positive culture was obtained and showed coagulase-negative *Staphylococcus albus*. It is possible, as has been suggested recently in a report from the Cleveland Clinic,[8] that too much blood was used and that the inherent bacteriostatic action of blood inhibited growth. The Cleveland report suggests that more success may be obtained with 2 or 3 c.c. of blood.

Cervical cultures were obtained in 38 cases. Cul-de-sac cultures of tubo-ovarian masses were available in 25 cases. In the latter group, four cultures were negative. All organisms present, according to Bergey's[9] "Determinative Bacteriology", are normally found in fæces. In no case in the retrospective or prospective series was the gonococcus recovered. This suggests that it plays little or no direct role as an etiological agent in the kind of pelvic inflammatory disease for which women require hospital admission. Complete details of culture findings are presented in Table I.

Papanicolaou smear results were available in 27 cases. Trichomonads and inflammatory cells were reported in the vaginal smears in 20 of these. Cervical smears uniformly contained a high content of fresh leukocytes. The vagina, however, appeared more resistant to infection and did not have marked evidence of inflammation until the higher infection was prolonged and severe. We used the method suggested by Wied[10] to locate the infection and estimate its severity in the lower genital tract by comparing the number and quality of leukocytes in the endocervix and vagina.

The endometrial biopsies obtained in the prospective series indicated this area to be relatively resistant to inflammation. Menstrual debris occasionally made interpretation difficult but the biopsy specimens usually contained some basal areas of endometrium. When the duration of the disease before treatment was prolonged, however, the endometrium, like the vagina, manifested pronounced inflammatory changes.

GENERAL TREATMENT

The principles of treatment were: (1) rest and supportive measures, (2) judicious and adequate use of antibiotic agents, and (3) drainage of pus when possible.

The oft-quoted words from John Hilton's "Rest and Pain", first published in 1863, would seem to represent one of the most important principles in the treatment of pelvic inflammatory disease: "Rest is essential to growth. We recognize this in the growing child where the one that sleeps most, usually thrives, while the wakeful, restless child seldom displays the evidence of active nutrition. What is true of growth is true also of repair. Repair is but a repetition of growth. The same elements, the same kindred conditions are necessary to the same results."

The response to treatment was always more rapid when the duration of disease before admission to hospital was short. Conversely, when symptoms had been present many days before the patient sought care, recovery was prolonged and measures such as use of parenteral fluids and long intestinal tube suction were frequently necessary.

Chloramphenicol and a penicillin-streptomycin combination were the antibiotic agents most commonly employed and most frequently effective.

OPERATIVE THERAPY

Colpotomy, when indicated, was always beneficial. This was carried out when there was a fluctuant tense "bulge" in the posterior fornix of the vagina that could be drained readily by a midline incision in the posterior vaginal vault between the utero-sacral ligaments, with no danger of spill into the general peritoneal cavity. A firm rubber drain, inserted in the abscess cavity and sutured to the colpotomy site, assured adequate drainage after the initial release of pus and disruption of loculations. Colpotomy was possible in six cases.

There was one death in the series. This was of an 18-year-old coloured woman who had severe recurrent disease. She was treated intensively with many antibiotics and finally was subjected to bilateral salpingectomy after being afebrile for eight days. Postoperatively she did poorly, developing a pelvic abscess and wound abscess, and ultimately expired on the twenty-first postoperative day. *Staphylococcus aureus* was cultured from the wound and it is quite possible that this was a superinfection due to prolonged use of antibiotics. Preoperatively and postoperatively she had received penicillin, streptomycin, chloramphenicol and nitrofurantoin. This case also illustrates that Simpson's criteria of operability in pelvic inflammatory disease probably apply as appropriately in the antibiotic era as they did when he originally laid them down in 1909.

SUMMARY

The typical patient with salpingitis is from the lowest socio-economic stratum of our society. Her hygienic habits are poor, and she has superstitions that preclude all bathing at the time of her menses. Moreover, the bathing facilities in her home, if present at all, are often shared by several other families. All of the above factors promote a luxuriant flora of bowel organisms in her vagina. Similar organisms occur in women of higher economic and educational status but not in such abundant numbers.[11] During the menses, when the hormonal support of the genital tract is at a low point, causing a drop in tissue resistance, and the bacteria-repelling propensity of the cervix is neutralized by the menstrual flow, susceptibility to an ascending infection exists. Presumably when the dose per unit of time is sufficient to overcome the resistance of tissues, even organisms of low virulence such as the bowel organisms will produce infection. The endometrium and vagina initially appear relatively resistant to the manifest effects of inflammation when compared with the endocervix and Fallopian tubes. In the untreated or late case, the endometrium and vagina will eventually show signs of inflammation.

It is evident that most cases of salpingitis, severe enough to require admission to hospital, are not due to the gonococcus but to the so-called "secondary invaders" present in sufficient numbers to take advantage of lowered tissue resistance.

Koch's first two postulates, that an organism, to be considered the etiological agent of a disease process, must (a) always be associated with the disease and (b) be isolated in pure culture, appear to exonerate the gonococcus and incriminate the bowel organisms in salpingitis.

Salpingitis invariably means an infection of the urinary tract as well.

Pregnancy wastage in this group is 34%.

An educational program, perhaps directed at the early teen-ager, expounding the principles of good perineal and body hygiene and exploding the various superstitions that discourage bathing during the menses could greatly reduce the incidence of salpingitis.

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RÉSUMÉ

L'auteur s'est proposé d'étudier les problèmes cliniques et étiologiques que présente la salpingite ainsi que son retentissement économique. D'après lui, la malade typique atteinte de cette affection appartient aux classes socio-économiques inférieures. Elle ne pratique qu'une hygiène primitive et croit encore qu'il ne faut pas se baigner pendant les règles. De plus, la chambre de bain rudimentaire de son logis (si chambre de bain il y a) est souvent partagée avec plusieurs autres familles. Tout favorise donc une croissance abondante de colibacilles dans la flore vaginale. Plusieurs femmes sont porteuses de colibacilles sans être atteintes de salpingite mais la concentration microbienne chez elles est moindre.

Lorsque la défense des voies génitales est affaiblie comme au temps des menstruations, par diminution des secrétions hormonales, ou que le col perd son imperméabilité par l'écoulement du flot cataménial, l'infection vaginale peut se propager vers l'intérieur. Dans ces circonstances, même les organismes de basse virulence peuvent causer de l'infection dès que, par leur concentration, ils surmontent la résistance des tissus. Même si l'endomètre et le vagin semblent au début relativement réfractaires à l'inflammation, comparés à l'endocol et aux trompes de Fallope, ils finissent à la longue par y succomber. La plupart des cas de salpingite dont la gravité justifie l'hospitalisation sont causés non pas par la gonocoque mais plutôt par une surinfection dite secondaire qui profite de l'épuisement des défenses naturelles des tissus. Le postulat de Koch en fait preuve. La salpingite implique invariablement une infection des voies urinaires; de plus, 34% de grossesses chez ces malades sont perdues. Comme dans de nombreux autres domaines, l'amélioration de la situation repose sur l'éducation du public et la réfutation de certaines croyances de bonne femme.

ARTERITIS IN RHEUMATOID ARTHRITIS*

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IN A 12-MONTH PERIOD we have had the opportunity of observing on our wards two patients with rheumatoid arthritis who developed signs of peripheral neuritis with bilateral foot drop, right wrist drop, pleuritis, and conjunctivitis; in one patient, pericarditis and multiple necrotic skin lesions were also present.

The signs and symptoms occurred while the patients were receiving some form of steroid therapy for their arthritis.

The clinical picture was similar to that described by Slocumb, Polley and Ward,[1] as manifestations of hypercorticism, and to the arteritis associated with rheumatoid arthritis noted by Schmid *et al.*,[2] Kemper, Baggenstoss and Slocumb,[3] and others.

Though the literature contains several references to these syndromes, these cases represent our first experience with this entity. It was therefore considered of interest to record these cases in some detail, noting the clinical course and some of the problems encountered in management.

CASE 1.—The first patient (G.W.), a 57-year-old electrician, developed arthritis in 1944, at the age of 43, with recurrent episodes in the fall of each year. In 1950 he suffered an acute attack of arthritis affecting all his joints, which remained generalized and active in spite of use of aspirin, intra-articular hydrocortisone, oral cortisone and gold injection. He was admitted to hospital on three occasions, in 1951, 1952 and 1957, with only transient improvement in his signs and symptoms.

In May 1957, he was discharged from hospital on 7.5 mg. prednisone and aspirin grains 40 daily, but continued to do poorly. In October 1957, he was started on a new steroid compound B†, 10 mg. per day, which was continued until his admission on January 8, 1958.

On admission the patient complained of severe stabbing left flank pain between the ribs and the iliac crest, aggravated by movement and respiration. One week before admission he had severe sharp sticking substernal pains which radiated to the right and left chest. Three weeks before admission bluish mottled discolouration was noted on both legs; this was more marked in the dependent position, and was associated with burning and paræsthesia. This discolouration of the legs became progressively worse, as did his arthritis in spite of the new steroid. He had no cough, hæmoptysis or sputum, or history of preceding upper respiratory infection.

Physical examination revealed a pale, febrile, extremely sick patient, practically immobilized because of chest and arthritic pain occasioned by the least movement. Fine moist rales and a pleural friction rub were noted in the left axilla. Blood pressure was 170/100 mm. Hg; pulse 110 and regular; and there were no cardiac murmurs or pericardial friction rub.

All the joints were affected and painful to varying degrees. There were no subcutaneous or perivascular nodules. All modalities of sensation of the lower legs and feet were markedly impaired. Knee jerk and ankle jerk were slightly depressed; muscle power was not impaired. There was slight ankle œdema, Homans sign was negative, and there was blotchy erythema and cyanosis of the lower legs that showed a reticulated pattern similar to that seen in livedo reticularis. The discolouration blanched on pressure and elevation of the legs. It is to be emphasized that the dorsalis pedis and posterior tibial arteries were easily palpable (Fig. 1).

Hæmoglobin value was 81%, erythrocyte sedimentation rate was 39 mm. in one hour, and white cell count 19,000. Urine was clear. Chest radiograph revealed slight haziness in the left base and a slight pleural effusion (Fig. 2). The electrocardiogram showed evidence in keeping with pericarditis. The patient was started on antibiotics and given anticoagulant therapy on presumptive evidence of phlebitis and low-grade pulmonary infection.

Five days after admission, while he was receiving anticoagulants, severe pleuritic pain occurred on the right side. Again there was no hæmoptysis and repeated sputum cultures were negative for pathogenic organisms. There was no objective evidence of phlebitis in the legs.

Substernal pain, pleuritic pain, hypoæsthesia and an erythematous lesion of the legs, electrocardiographic evidence of pericarditis, and x-ray evidence of pleuritis suggested the possibility of disseminated lupus erythematosus or polyarteritis.

The latex test for rheumatoid activity was strongly positive to a titre of 1:5120, but repeated search for

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†Experimental drug: 6 chloro-hydrocortisone.

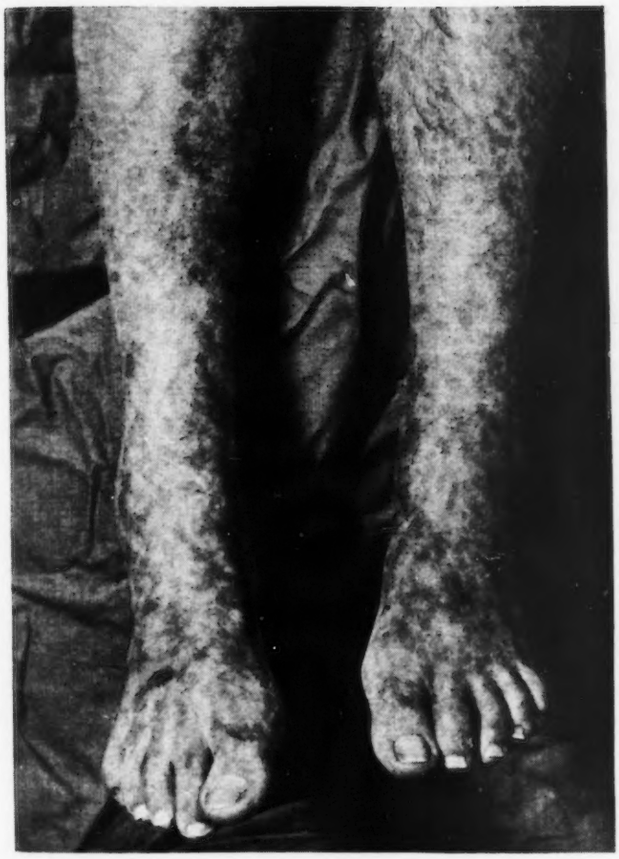

Fig. 1.—Patient G.W. Legs dependent, showing diffuse livedo reticularis type of mottling.

L.E. cells was negative. The Wassermann reaction was at all times negative.

Fig. 3 summarizes in graphic form the patient's course in hospital.

On admission there were marked pyrexia, arthritis, pericarditis, pleuritis, hypoæsthesia and blotchy erythema and cyanosis of the legs.

Compound B was discontinued on admission and he was given prednisone 5 mg. t.i.d. for four days, at which time it was discontinued as the signs and symptoms persisted and the possibility of hypercorticism was considered. ACTH (Duracton), 40 units per day, was started 10 days later and produced an abrupt fall in temperature and a decrease in stiffness; evidence of pleuritis and pericarditis subsided. Hypoæsthesia persisted in the lower legs. Marked conjunctivitis and episcleritis developed in the left eye, and a marked erythematous blush was noted over the sternal region. Gastro-intestinal bleeding occurred on the seventh day of ACTH therapy. The hæmoglobin level dropped to 55%, but improved when the patient was given an ulcer regimen; ACTH was continued at a lower dosage.

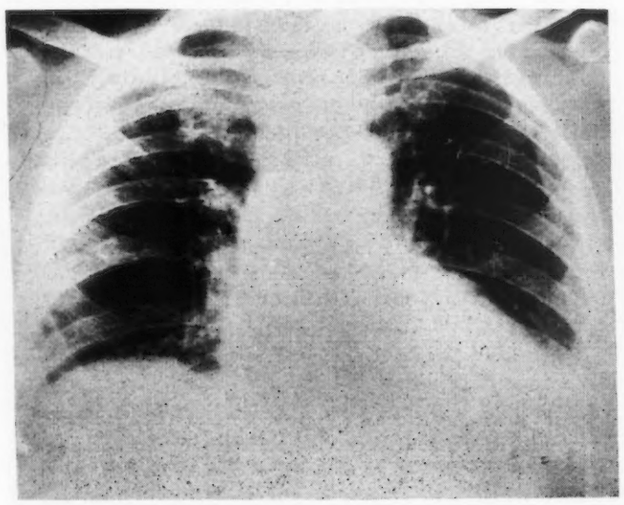

Fig. 2.—Patient G.W. Pleural effusion left base.

During the next five weeks the patient remained in a relatively quiescent state, except for an occasional spike in temperature and persisting arthralgia as the ACTH dosage was tapered off.

Chloroquine was added to the treatment program in an effort to control the arthralgia, with little effect.

After two months in hospital the patient improved somewhat and was walking about. Prednisone 10 mg. per day was resumed in the first week in March as maintenance therapy before discharge from hospital. On the fifth day after reinstitution of prednisone therapy, the patient wakened with weakness and loss of control of his right wrist, and marked wrist drop was noted. Prednisone was discontinued and the dosage of ACTH was increased. Nine days after the onset of wrist drop, bilateral foot drop developed with absent ankle jerks and complete loss of sensation to all modalities below the ankle. At first the L4-L5 dermatomes appeared involved, and then a glove and stocking type of anæsthesia developed in both feet. ACTH dosage was gradually tapered off and stopped; this resulted in an increase in temperature, stiffness and arthralgia in spite of increasing aspirin dosage.

At the time of onset of paresis, and while steroid therapy was continuing, the patient complained mostly of muscle ache, while the arthralgia was only moderately troublesome. When ACTH was stopped, muscle ache, stiffness and arthralgia increased markedly.

Several muscle biopsy specimens in February and March showed areas of lymphocytic infiltration. Arterioles were normal and in one section lymphocytic infiltration was seen around a venous blood vessel.

Since the completion of this chart (Fig. 3), the patient has not been taking steroids for 12 months and has been maintained on aspirin grains 100 daily and codeine grain 1/8 as required. He continues to run a low-grade fever, and has two-plus arthralgia, but no muscle stiffness; blotchy erythema of the legs persists though less florid. There was only slight return of sensation in the wrist, hand and feet, and only minimal motor function nine months after the onset of the paresis. The neurological signs cleared completely in the subsequent three months.

There is still marked rheumatoid activity as evidenced by the positive latex fixation test of 1:5120 dilution, C-reactive protein 6+, and marked elevation of the mucoproteins to 184, 139, and 402 mg. % on several determinations.

CASE 2.—The second patient (W.H.), a 58-year-old man, was first admitted to Queen Mary Veterans Hospital in August 1947, with a history of recurring backache of three years' duration and of recent painful swelling of hands, knees, elbows, wrists and right shoulder; subcutaneous nodules and gross evidence of arthritis were noted. Hæmoglobin value was 89% and

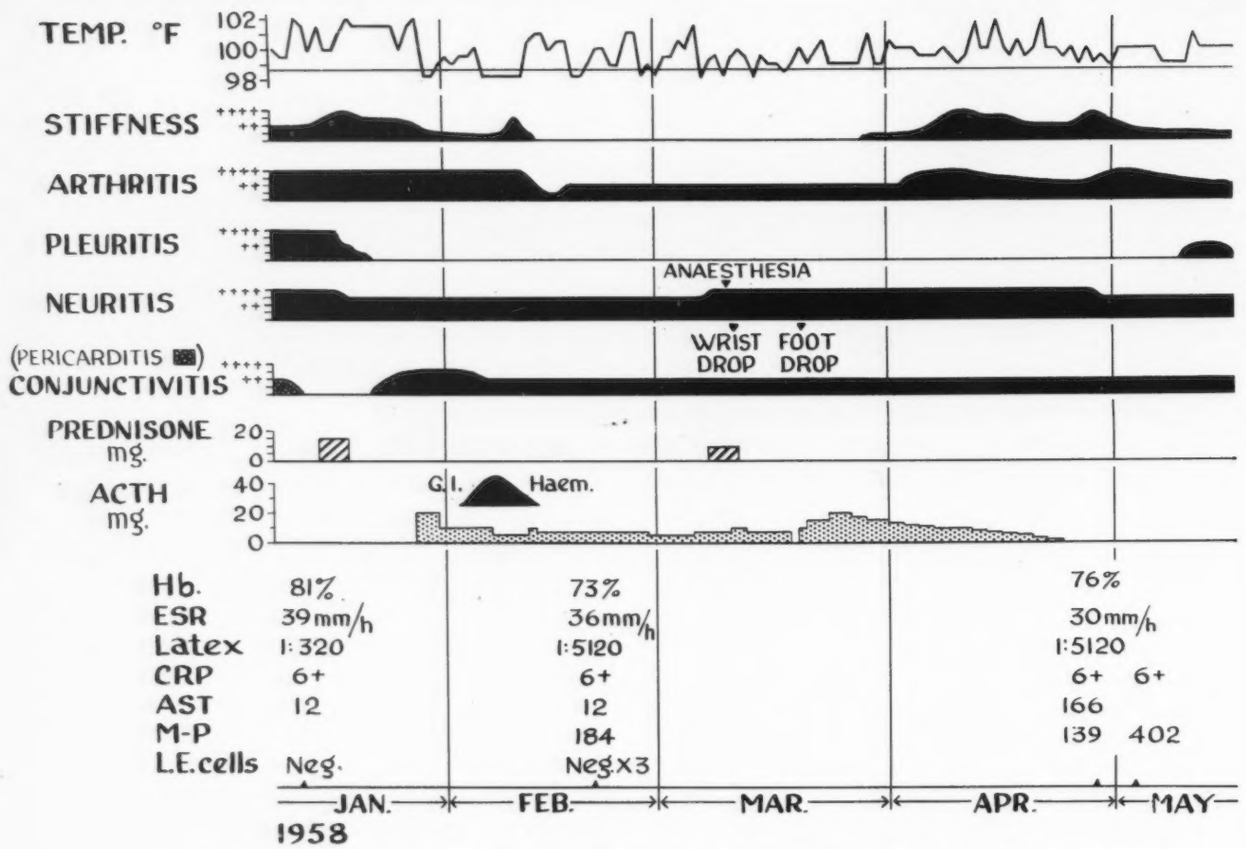

Fig. 3.—Male, G.W., aged 57. Patient's course in hospital. Note that the onset of wrist drop and foot drop occurred after the reintroduction of prednisone in March 1958. C.R.P. = C-reactive protein. AST = antistreptolysin titre. M-P = mucoproteins (100 mg. % = N).

erythrocyte sedimentation rate (ESR) was 40 mm. in one hour.

He was given intramuscular gold, and developed a petechial rash four days after the onset of therapy, which subsided on administration of antihistamines without interruption of the gold injections. At time of discharge, in February 1948, six months later, the ESR was 2 mm. in one hour, and the arthritis was in remission. Gold therapy was continued for 42 months to a total dose of 4325 mg. It was temporarily discontinued for a two-month period, September-October 1951, because of another skin eruption. During this period his joints were relatively quiescent.

In October and November 1952, the patient had two episodes of left pleuritic chest pain for which no cause could be found. From May 1952 to September 1954, the patient had minimal arthritic complaints. In September 1954, he was given cortisone acetate, 25-75 mg. per day, and has been maintained on steroids to this present admission. In spite of steroid therapy, joint pains gradually increased and he was forced to stop work in February 1957. At this time he was changed over to prednisone, which was increased to 10 mg. daily, and butazolidine 200 mg. b.i.d. was added. He complained of increasing pains in all his joints—cervical spine, shoulders, elbows, wrists, knees, ankles, lumbar spine—and of swelling of the legs up to the knees; there was no dyspnœa. He was readmitted to Queen Mary Veterans Hospital on August 20, 1957.

On physical examination, he was a well-developed, well-nourished male, in great distress, barely able to get in and out of bed, or feed or dress himself. There were occasional crepitations at both bases. Blood pressure was 130/80; pulse 90 and regular. The nervous system was normal. There was marked œdema of the legs. Gross rheumatoid changes were noted in the above-mentioned joints. Hæmoglobin value was 96%, ESR 39, WBC 11,200; urine, serum proteins, chest radiograph, and ECG were normal.

Fig. 4 summarizes this patient's course in hospital.

The patient was started on 20 mg. prednisone, which resulted in a lowering of the temperature and improvement of joint pain. Three weeks later, in mid-September, pyrexia recurred in spite of continued therapy with prednisone. Arthralgia and stiffness increased. ACTH, 20 units per day, was given, which resulted in a return of the temperature to normal and considerable decrease in subjective complaints of pain and stiffness. The patient remained afebrile with mild arthralgia through October, November and December 1957 when he was receiving prednisone 15-20 mg. and phenylbutazone 200 mg. per day. He continued to look ill and pale. Œdema of the legs persisted, and failed to respond to salt restriction and administration of mercurials. *November 12*: While receiving 20 mg. prednisone, he developed left pleuritic pain, aggravated by respiration. Slight cough and hæmoptysis were noted. Fine crepitations and a friction rub were present in this region. Radiography revealed increased markings and some fluid at the left base. Infarct or pneumonitis was considered the most likely diagnosis.

December 20: While still taking prednisone, he developed severe pain in the right foot and calf; phlebitis was again suspected. The patient was given anticoagulants, prednisone was increased to 25 mg.

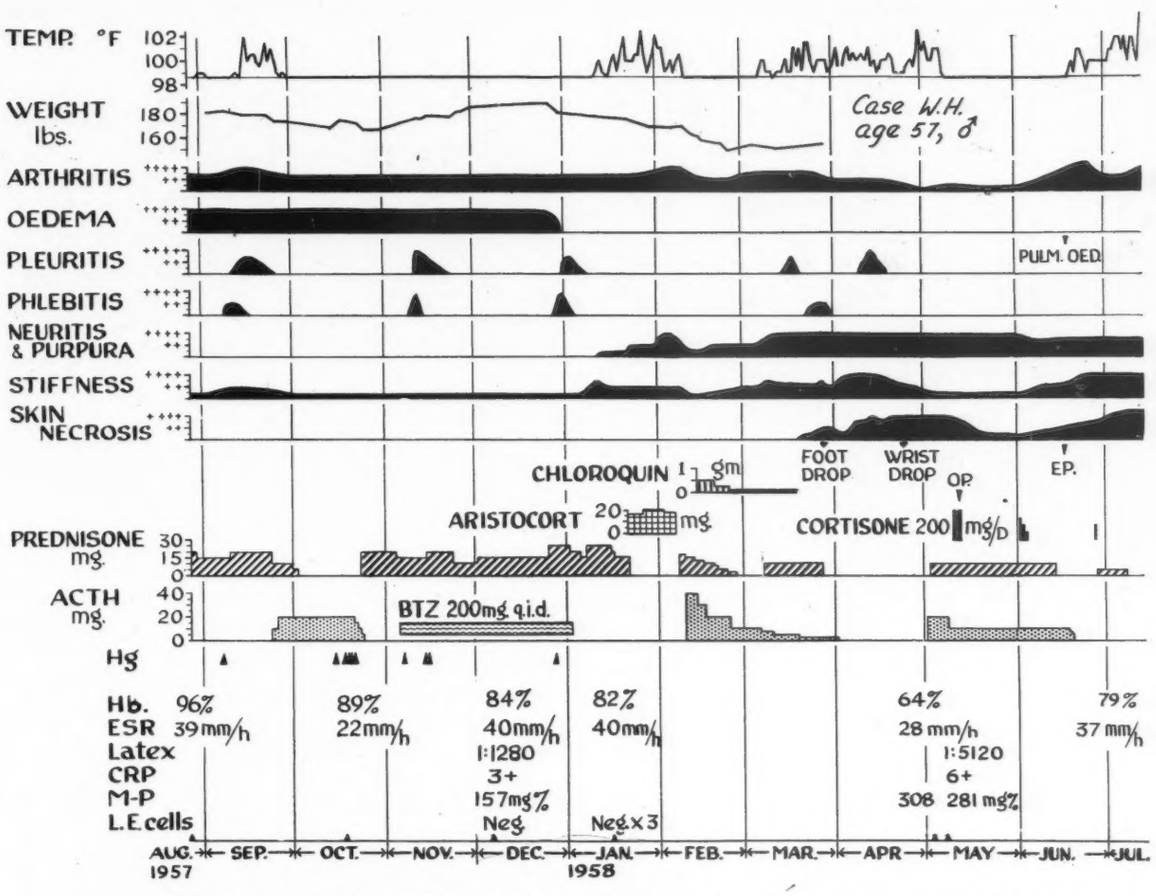

Fig. 4.—Male, W.H., aged 58. Patient's course in hospital. Note episodes of pleuritis and phlebitis (pain in legs). Onset of severe neuritis and purpura after administration of tramcinolone in January 1958. Foot drop and wrist drop developed after reintroduction of prednisone in March 1958. CPR = C-reactive protein. M-P = muco-proteins. L.E. = lupus erythematosus cells.

per day, and phenylbutazone was discontinued. At this point the patient suddenly responded to use of mercurials, and the œdema of the legs subsided, associated with marked drop in weight.

January 7, 1958: The patient complained of increasing stiffness and calf tenderness, pyrexia recurred, and the temperature rose to 102° F., which in retrospect appeared to follow the period of increased prednisone dosage. *January 22*: It was decided to try triamcinolone (Aristocort) 16 mg. per day, a more potent steroid with less sodium-retaining action, in an effort to control his symptoms. Pyrexia persisted. *February 1*: There was marked increase in arthralgia and stiffness; paræsthesia, burning feet, numbness and hypoæsthesia of the toes developed. A marked petechial eruption developed on both legs, with several large bullous erythematous areas (Fig. 5). Triamcinolone was discontinued and prednisone restarted and tapered off; then ACTH, 40 units daily, was given. Within 24 hours of giving ACTH, the temperature, arthralgia and stiffness had subsided considerably. A muscle biopsy on *February 14* failed to give evidence of arteritis. ACTH was then gradually decreased because of development of moon facies and salt retention; the arthralgia and stiffness recurred.

Though we were aware of the possible relation of steroids to the development of peripheral neuropathy, prednisone 10 mg. per day was restarted on *March 6* in the hope of controlling the arthritis while the ACTH was being discontinued. Within two days of restarting prednisone the temperature rose, muscle ache increased and chills and left-sided chest pain occurred: On the ninth day of prednisone therapy necrotic skin lesions appeared on the periungual regions of the toes, heel, right forearm and back. Phlebitic pain in the legs recurred. On the sixteenth day the patient awakened with bilateral foot drop, and prednisone was discontinued.

Chest pain with patchy infiltration on the right and left side with a left-sided effusion was noted on *April 14*. This cleared in one week. Twenty-three days after cessation of all steroid therapy, and 28 days after foot drop was noted, the patient developed weakness and wrist drop of the right hand. Necrotic lesions became more numerous. The lesion of the left heel and calf became infected and extended to the deep tissue of the leg. It is of interest to note that muscle ache and stiffness were more prominent than arthralgia during this period.

On *May 1*, the patient was deteriorating rapidly and was almost moribund while not receiving steroids. ACTH 20 units per day and prednisone 10 mg. per day were restarted in an effort to reverse the downhill course. Low plasma hydroxycorticoid levels in spite of administration of ACTH suggested the presence of adrenal unresponsiveness due to prolonged steroid therapy.

The necrotic skin lesions grew proteus and coliform bacteria, sensitive to streptomycin, but the leg became more œdematous and inflamed in spite of therapy, and a deep fascitis developed. The leg was widely opened to allow drainage. This together with blood

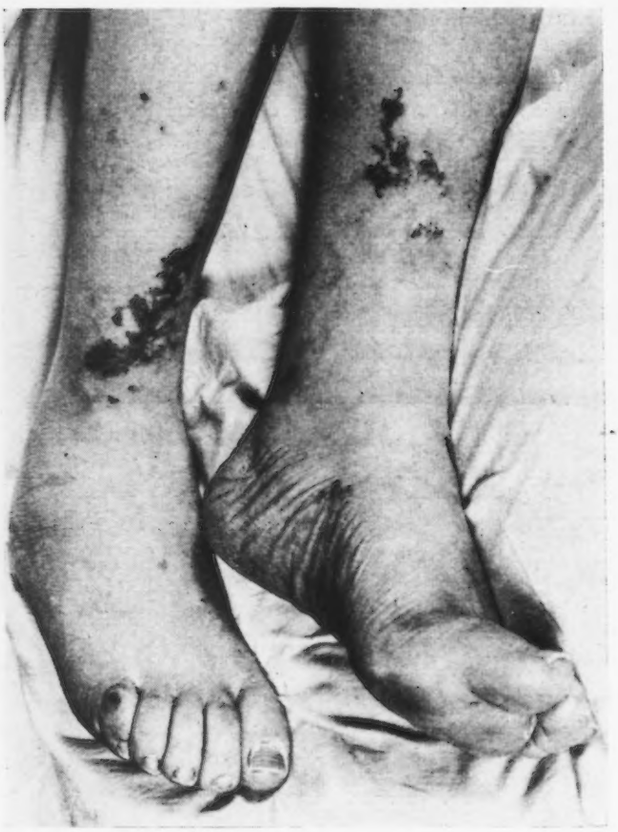

Fig. 5.—Patient W.H. Eight days after beginning triamcinolone, eruption developed on both legs. Erythema multiforme type lesions with hæmorrhagic bullous blebs in the central portions. These healed slowly, leaving deep pigmented scars.

transfusion and administration of an antibiotic appeared to arrest the progressive course.

The patient was receiving 10 units of ACTH and 10 mg. of prednisone per day. No new skin lesions appeared and the older lesions appeared to be granulating in. The patient was somewhat improved. Foot drop and wrist drop persisted and there was only minimal return of sensation in spite of vitamin B_{12} and thiamine therapy.

The hæmoglobin level dropped from 98 to 64% at the lowest point, and the ESR remained relatively unchanged. A latex fixation test showed a marked rise and was positive to a titre of 1:5120; the C-reactive protein value was 6+ and the serum mucoproteins 200-300 mg. %. Numerous examinations of LE preparations were negative. The patient remained in a steady state through the month of June, receiving prednisone 10 mg. per day and ACTH 5 units b.i.d. Attempt at skin closure of the leg wound was unsatisfactory. Early in July, he developed acute pulmonary œdema. This was considered to be due to ACTH therapy with inadequate salt restriction. Epileptic seizures followed, without evidence of localizing signs on EEG. These were controlled with phenobarbitone.

ACTH and cortisone therapy were stopped because of the possible relationship of this medication to these new symptoms. After the epileptic fits the patient remained confused, disoriented and lethargic.

Joint pains, muscle ache and fever increased. New necrotic skin lesions appeared in the toes of both feet, which became progressively gangrenous in spite of vigorous pulsations in both dorsalis pedis vessels (Fig. 6). Gangrenous changes of the little finger of the right hand also developed.

The patient deteriorated slowly, with increasing gangrene of toes, toxæmia, pyrexia, arthralgia uncontrolled by codeine and meperidine, and progressive abdominal distension. He died quietly in his sleep 11 months after admission to hospital.

Permission for complete post-mortem examination was not granted. Multiple needle biopsies only were permitted. These were obtained from the lung, liver, kidney, pleura, skin and the muscle of both legs. Several arterial lesions were found in the biopsy section taken from the calf muscle and skin of the left foot (Figs. 7 and 8). Fibrinoid necrosis and polymorphonuclear and round cell infiltration were noted throughout the vessel wall, a lesion consistent with that seen in periarteritis nodosa.

DISCUSSION

Both patients were similar in many respects—both were men in the 50-60 age group with progressive rheumatoid arthritis of 15 years' duration that responded poorly to therapy. The first patient (G.W.) had been receiving steroids for six months and the second patient (W.H.) for three years, when signs of neuropathy associated with other systemic manifestations of rheumatoid disease developed.

In each case the use of a more potent steroid, compound B (in Case 1) and triamcinolone (in Case 2), resulted in marked aggravation of the signs and symptoms.

The earliest signs were burning paræsthesia, œdema and hypoæsthesia of the legs, which were present for 4-6 weeks before admission to hospital. Evidence of pericarditis was noted in G.W. (Case 1), and pleuritic pain occurred on several occasions

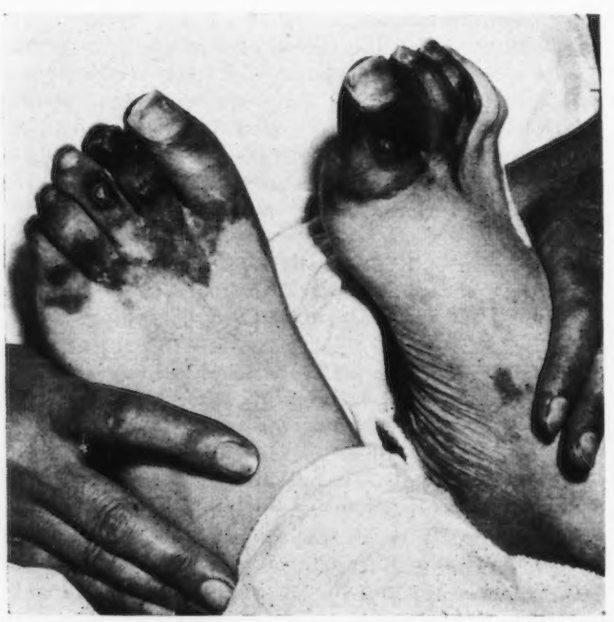

Fig. 6.—Patient W.H. Progressive gangrene of toes of both feet. The dorsalis pedis and post-tibial vessels of both feet were readily palpable.

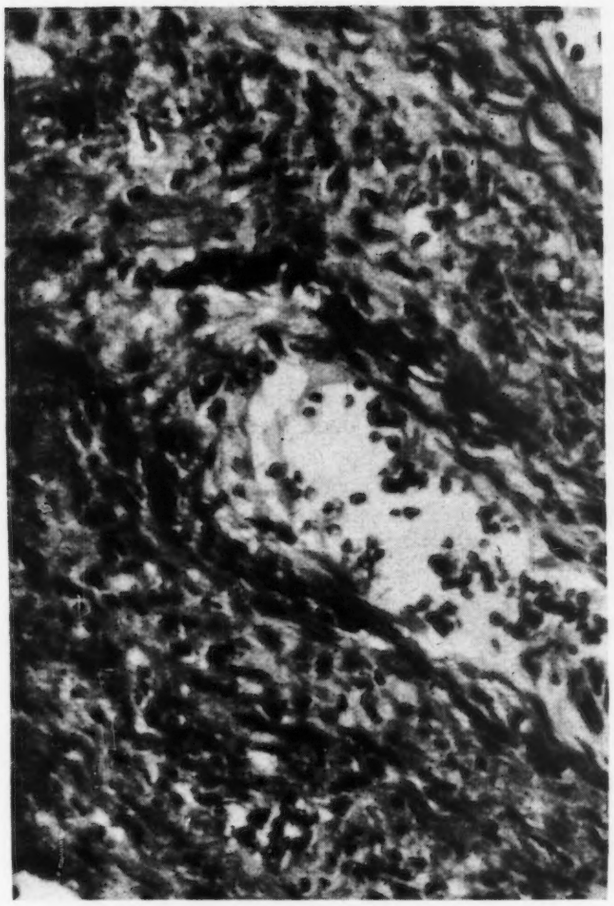

Fig. 7.—Patient W.H. Skin biopsy showing smudgy necrosis of the muscle wall with some infiltration by polymorphonuclear and round cells. × 200.

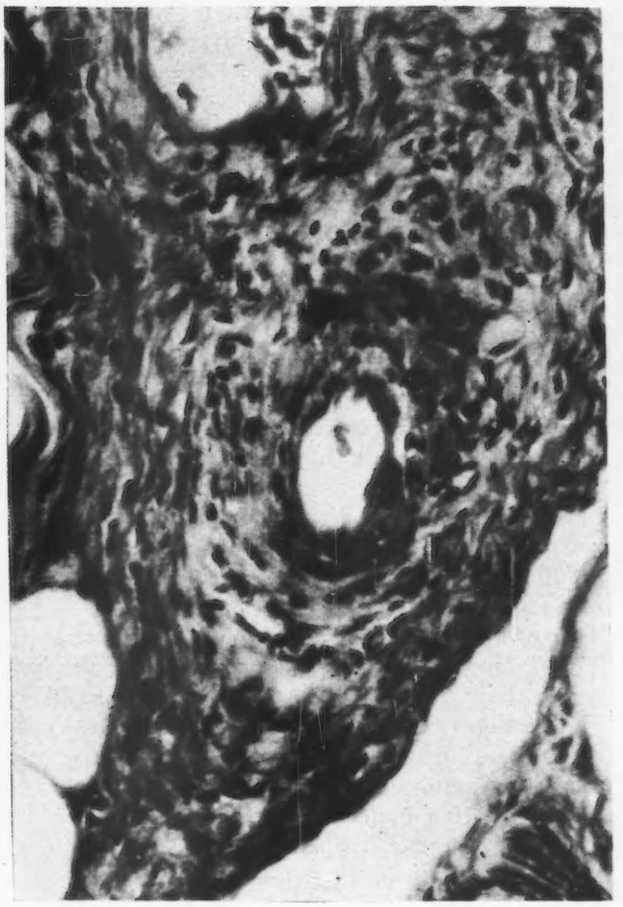

Fig. 8.—Patient W.H. Muscle biopsy of right calf, showing fibrinoid necrosis in the muscle layer of a small arterial vessel and polymorphonuclear and round cell infiltration through the muscle layer. × 200.

in both patients. Œdema and pain in the legs suggested the presence of phlebitis, but it was difficult to determine whether this was true phlebitis or whether the pleuritic pains were spontaneous inflammatory lesions of the arthritic process—so-called "rheumatoid lesion"—or a secondary manifestation of pulmonary embolization.

Marked myalgia and stiffness developed. Hypoæsthesia and weakness progressed, giving rise to foot drop and followed by wrist drop in Case 1, and to wrist drop followed by bilateral foot drop in Case 2. In Case 2 multiple spontaneous necrotic skin lesions developed which became secondarily infected and showed evidence of delayed healing.

The clinical features of prolonged corticoid therapy in rheumatoid arthritis of myalgia, fatigability, pleuritis, pericarditis, œdema, phlebitis, polyneuritis and necrotic skin lesions are similar to those described by Slocumb, Polley and Ward,[1] in the hypercorticism syndrome. Similar diffuse parenchymal involvement has been noted in patients with periarteritis nodosa, disseminated lupus erythematosus, and malignant arthritis before the advent of cortisone. In the case of rheumatoid arthritis, Slocumb and more recently Kemper, Baggenstoss and Slocumb,[3] Bevans *et al.*,[8] Levin *et al.*[9] and others have attributed these lesions to the use of cortisone.

Thus Slocumb, Polley and Ward[1] found a higher incidence of these lesions in patients receiving cortisone with symptoms of hypercorticism than in patients not receiving steroids.

Kemper, Baggenstoss and Slocumb,[3] in reviewing post-mortem findings in 118 cases of rheumatoid arthritis, found 14 cases of arteritis, four of which had received cortisone.

Other reports of acute arteritis have appeared in the literature. In most of these cases, clinical manifestations of diffuse arteritis appeared during administration or shortly after withdrawal of cortisone or ACTH therapy.[3-8, 10, 11]

Both the patients reported in this paper developed manifestations compatible with diffuse arteritis while taking steroids.

When the occurrence of peripheral neuropathy suggested the possibility of hypercorticism, reduction of steroid dosage was attempted. Frequent alteration of the dosage of ACTH and prednisone was tried with little apparent effect on the rate at which the patient could be weaned off steroids. This is in keeping with the observation of Slocumb that "the use of hydrocortisone, prednisone, prednisolone or corticotrophin either as alternative to or concomitantly with cortisone has not shortened the time required for recovery from over-dosage".

It is of interest to note that though steroids were gradually discontinued after the first manifestations had appeared, the neuropathy and skin lesions progressed.

While the first patient was completely weaned off steroids, as is recommended for the treatment of hypercorticism, without ill effect, in the second patient it was extremely difficult to control the systemic manifestations of the disease adequately. When steroids were completely stopped, marked deterioration occurred with pyrexia, arthralgia and progression of spontaneous necrotic skin lesions.

In spite of the possible causal relation between ACTH and cortisone and the manifestation of hypercorticism, steroid therapy was resumed as a desperate measure in an almost moribund patient (Case 2). Dramatic improvement occurred, and new lesions failed to develop. Adrenal insufficiency was considered to have resulted from prolonged prednisone therapy so that replacement therapy was required.

Slocumb noted that it makes little difference in regard to the development of hypercorticism, which steroid is used, that the patients most likely to develop this syndrome are females with rheumatoid arthritis or disseminated lupus, and that it develops more frequently when steroid dosage is being increased but may occasionally be seen when relative hypoadrenalism is produced by sudden withdrawal of steroids.

The clinical picture of multiple system involvement suggested the possibility of lupus erythematosus. A high incidence of positive LE cells has been noted in this type of patient by Ogryzlo[4] and Slocumb and his colleagues.[1] Repeated examination of LE preparations in both these patients was negative.

Multiple muscle and skin biopsies failed to reveal any evidence of true arteritis.

In patient G.W. a single lesion was noted of a perivenous infiltration of lymphocytes. In the second case a true arteritic lesion was noted. Neuropathy and skin lesions have been noted in rheumatoid arthritis before the advent of cortisone. Kemper, Baggenstoss and Slocumb,[3] in a review of the literature noted many reports of neuropathy and vascular lesions in patients with rheumatoid arthritis. They divided the vascular lesions into three types: (1) perivascular and adventitial accumulation of leukocytes and plasma cells, without necrosis; (2) subacute arteritis with infiltration of lymphocytes, leukocytes through all layers of the vessel wall and some exudation of fibrin; (3) acute arteritis with infiltration of polymorphonuclear cells and necrosis of the vessel wall in one or more organs, joints, heart and subcutaneous nodules.

The biopsy finding in patient G.W. would fall into Group 1 which is considered to be a nonspecific manifestation. The presence of arteritis, however, cannot be ruled out. Cases have been reported where muscle biopsies have been negative before death, arteritis being found only after extensive search in multiple sections of various tissues, as noted in Case 2.

There are numerous reports in the literature[12-17] of arterial lesions in rheumatoid arthritis. Most of these lesions are perivascular or adventitial infiltration without necrosis, falling into Kemper's Groups 1 and 2, occurring in patients who have not received cortisone.

True arteritis with necrosis of the vessel wall has also been reported in rheumatoid arthritis.[2, 7, 11-13] In a review of 118 autopsies on patients with rheumatoid arthritis Kemper found 14 with necrotic arterial lesions. While he emphasized that four patients had received cortisone (an incidence of 30%), one cannot escape the fact that 10 patients had not received steroids. Cruickshank[13] reported one of six patients, Robinson[5] one of four, and Schmid *et al.*[2] three of six patients who showed arteritis without having been on steroids. The 30% incidence noted by Kemper and his colleagues[3] is, however, considerably in excess of the 10% incidence noted by Sokoloff, Wilens and Bunim[12] in a group of rheumatoid patients who had not received steroids.

Whether arteritis observed in these patients is due to the disease process itself or is a manifestation of cortisone therapy is not completely resolved. Steroids would not appear to be essential for the production of these arterial lesions in rheumatoid arthritis. The evidence at present suggests that in patients showing arteritis, as in Kemper's Group 3, an increased incidence of pre-treatment with cortisone is found, and that use of steroid may accelerate the development of arterial changes already present.

It is impossible to predict which patients will develop this so-called "pan-mesenchymal reaction".

Thus the first patient (G.W.) received steroids for six months, and had no previous history of allergy or systemic signs apart from arthralgia. The second patient (W.H.), taking steroids for three years, developed several skin eruptions from gold therapy and on two occasions he developed unexplained pleuritic pain which may have been due to involvement of the pleura by the rheumatoid process. Kemper noted "no significant differences in the group with and without arteritis, with regard to onset, manifestation, severity, progression of their arthritis and treatment record, except for cortisone".

It would appear that those patients most severely affected with arteritis are likely to be put in hospital and given some form of steroid therapy. With newer and more potent steroids being synthetized, it will be a great temptation to try these drugs on patients who are doing poorly on other forms of treatment. It is this group of patients who run the greatest risk of developing this complication of steroid therapy.

The principles of therapy may be briefly outlined as follows: (1) Awareness of the possible

development of hypercorticism. (2) Early recognition, in terms of mood changes, fatigability, muscle ache, neuropathy, phlebitis, pleuritis and episcleritis. (3) Gradual reduction of steroid dosage, which must be carried out extremely slowly. It is important not to go too fast, as sudden reduction of dosage may give rise to relative adrenal insufficiency which may cause an exacerbation of the process. It is this aspect which resulted in the considerable juggling of steroid dosage as seen in these two cases. (4) It is important to get the patients' co-operation, as they are alarmed at the thought of discontinuing steroid therapy. (5) The syndrome of hypercorticism is most likely to develop when large doses of steroids are used. It has been recommended that one should not exceed 15 mg. of prednisone or 50 mg. of cortisone acetate in the treatment of rheumatoid arthritis. If improvement does not occur, other measures such as extra rest, physiotherapy, and use of aspirin or gold injection should be added to the treatment program.

SUMMARY

Two patients with rheumatoid arthritis are reported who developed neuropathy with bilateral foot drop and right wrist drop while receiving steroid drugs. Pleuritis, pericarditis, phlebitis and necrotic skin lesions suggest the presence of a diffuse arteritis in spite of negative results from muscle biopsy during life. The clinical course in the two patients suggests that therapy with steroids may have been an important factor in precipitating this syndrome. The difficulties in management and some of the complications have been noted.

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RÉSUMÉ

Les auteurs décrivent en détail deux cas de polyarthrite chronique évolutive chez des malades atteints de cette affection depuis une quinzaine d'années et dont le traitement n'avait pas été des plus satisfaisants. Après six mois et trois ans respectivement de traitement aux stéroïdes on observa chez eux des manifestations de névrite périphérique, de pleurite, de conjonctivite, de péricardite et enfin, chez l'un des deux, de nombreuses lésions nécrosantes de la peau. La substitution d'un composé plus puissant à la cortisone accentua considérablement les symptômes. Bien que les manifestations de ces complications puissent relever d'une artérite diffuse probablement le résultat d'hypercorticisme, la preuve est loin d'en être complète. En dépit de la fréquence de la lupoviscérite dans ce genre de cas, on ne put démontrer de cellules de Hargraves chez ces deux malades. Les auteurs soulignent l'importance de dépister ces complications dès leurs premières manifestations. On doit alors procéder à une diminution très lente de la posologie afin d'éviter l'insuffisance surrénalienne. Il est d'ailleurs prudent dans le traitement de la polyarthrite chronique évolutive de se limiter à des doses raisonnables de stéroïdes telles 15 mg. de prednisone ou 50 mg. d'acétate de cortisone.

THE CURABILITY OF CANCER OF THE RECTUM*

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CONSIDERABLE misunderstanding exists as to the actual curability of cancer of the rectum. At the Metropolitan General Hospital in Windsor, in its first eight years, a meagre total of 11 of these patients were admitted. In Windsor, before 1936, inasmuch as a single, and not particularly adequate, attempt was made to remove a cancer of the rectum, it is reasonable to conclude that cancer of the rectum was considered incurable. Subsequently, 371 patients with cancer of the rectum have been admitted to our Cancer Clinic. Opening of the clinic has changed our attitude towards this disease; and it is now frequently said that these patients have an unusually favourable prognosis. Neither of these conclusions is correct, and cancer of the rectum still remains a serious and all too frequently lethal disease.

In assessing results of treatment of cancer of the rectum one must remember that the surgeon deals with more or less selected individuals, already chosen by their family physicians as suitable for radical surgery. Conversely, the radiotherapist seldom has the opportunity to treat other than those in the inoperable or poor-risk group. Utilizing both surgery and radiotherapy, we receive patients from each category, as well as those with recurrent cancer after operation elsewhere. Even our series, however, like that of other cancer clinics, does not present a strictly true picture of cancer of the rectum as it exists in the community, but consists instead of a group from which some of the more

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TABLE I.—Status of Patients with Cancer of the Rectum

		5 years			10 years			15 years			20 years		
	No.	*Alive*	*Died cancer*	*Intercurrent disease*	*Alive*	*Died cancer*	*Intercurrent disease*	*Alive*	*Died cancer*	*Intercurrent disease*	*Alive*	*Died cancer*	*Intercurrent disease*
1935 to 1938	28	3	24	1	3	0	0	3	0	0	1	0	2
1939 to 1943	53	13	40	0	9	2	2	6	1	2			
1944 to 1948	84	35 42%	42	7	28 33%	4	3						
1949 to 1953	89	35 39%	48	6									
Total	254	86 34%	154	14	40 24%	6	5	9	1	2	1	0	2

Three patients in the 1935-1938 series lived five years; they were still alive at 15 years and ultimately died of intercurrent disease, two in the seventeenth and the remainder in the twenty-first year.

Of 13 five-year survivors in the 1938-1943 group, nine were alive at ten years. Two died of intercurrent disease between the fifth and 10th years and two of cancer in the sixth and seventh years respectively. Six are still alive after 15 years, one of the others having died of cancer in the 13th year and the remaining two of intercurrent disease in the 11th and 15th years, aged 74 and 88 years respectively.

In the 1944-1948 group of 35 patients who survived five years, 28 are alive after ten years; four have died of the cancer—two in the sixth year and one each in the seventh and 10th years respectively; three died of intercurrent disease between the fifth and 10th years.

favourable patients had already been removed by other surgeons, and to which a number of previously unsuccessfully treated patients have been added. Follow-up information is available on all our patients. Eighty-six of the 254 patients seen before 1954 lived five years, with no deletions for failure to accept treatment, for unfinished treatment, loss from old age or intercurrent disease. Twelve per cent of those seen between 1935 and 1938 survived; since 1943, 40% lived five years. The absolute five-year survival for the entire series is 34%. Forty patients (24%) lived for 10 years. It would appear that the patient who survives five years has an 88% likelihood of not dying of his cancer during the next five years, but cannot invariably be considered cured even after 10 or 15 years.

Although the first symptom was often sufficiently alarming to warrant immediate attention, the average patient delayed nine months before reporting. The four physicians whom we have had as patients were no exceptions and, indeed, actually delayed longer than did the average before seeking treatment. The loss in time was largely, but not entirely, the patient's responsibility. Attending physicians missed the diagnosis disturbingly often. We found that while 49% of the patients with cancer of the rectum were referred for treatment within one week of the original medical consultation, the cancer was not discovered in 22% for an additional period of from three months to two and one-half years. Our physician patients were unduly unfortunate in this respect also. With reasonable co-operation, however, the diagnosis is not difficult to establish. In properly prepared patients, 90% of these tumours were palpable to the examining finger, and 98% were within reach of the sigmoidoscope. On the other hand, a barium enema and x-ray examination not infrequently fails to demonstrate low-lying or ampullary cancers.[1]

It is possible to remove most cancerous rectums with, if need be, the attached uterus or portions of the vagina and bladder or prostate, but it is of doubtful advantage to cut one's way through tumour that is densely adherent to the pelvic walls. Such operations may cause more harm than benefit, and more satisfactory methods of treatment are available. On the other hand, a solitary liver metastasis does not contraindicate a resection, and worth-while relief is obtained not only from the distressing rectal symptoms but psychologically as well.

Our technical methods and criteria of operability have changed. Originally we deemed 60% of the tumours inoperable; later we were resecting 84%. Fixation of the tumour to surrounding structures was no longer considered a contraindication to successful operation; neither is old age. More recently the proportion resected has, with benefit, been reduced to 70%. The advent of chemotherapy, particularly in the preoperative preparation of the patient and availability of antibiotics, has aided in a reduction of the hospital mortality. Spinal anæsthesia has been used throughout, but developments in this field likewise have been of material aid.

TABLE II.—CANCER OF THE RECTUM—100 CONSECUTIVE PATIENTS

				Not treated		*Exploratory*		*Resected*			*Alive 5 years*
Recurrent	5			2		1		2			1
Primary	95	Inoperable	18	Too advanced	8	<3000 r t.d.	4		Colostomy	2	0
				Systemic reasons	10						
						<3000 r t.d.	6				0
						>3000 r t.d.	3				1
		Deemed operable	77	Local treatment	3						
						Surgery	1				1
						Fulg. + G.S.	1				1
						Fulg. + x-rad.	1				1
				Refused operation	5						
						Not treated	2				1 (with cancer)
						Irradiated	3				2 (with cancer)
				Explored, not resectable	9					3	0
				Resected.....	60	Hosp. mortality	4				31
Total	100									5	39 (14 without a colostomy)

Colostomy was required in five of the 35 patients in whom the tumour was not removed. In the absence of complete or impending obstruction, a colostomy plays little or no part in the palliative treatment of carcinoma of the rectum. Any benefit to be obtained thereby can be more satisfactorily received from external irradiation by conventional x-ray therapy or preferably by treatment with the cobalt beam.

Increased familiarity with the disease and in the care of these patients is by no means an unimportant factor.

100 CONSECUTIVE PATIENTS

For these reasons it would seem that more useful information might be obtained on the present status of cancer of the rectum by detailed study of a limited number of patients, rather than of the entire series. One hundred consecutive patients admitted between January 1, 1946, and early 1952, have been chosen. Their age on admission varied from 32 to 97 years. Thirty-nine of the 100 patients were alive at the end of five years.

Recurrent Cancer

Five of the 100 patients had recurrent cancer after operation elsewhere. Three with extensive liver metastases received no treatment but the remaining two were deemed worthy of an attempt to cure. One, after a perforation of the recto-sigmoid, underwent an anterior resection with restoration of continuity. Cancer recurred in the rectal stump within nine months.* After failure to control the tumour by 400 K.V. irradiation and intra-rectal radium therapy in a second clinic, we performed, unsuccessfully, a wide abdomino-perineal resection, hysterectomy and ureteral transplantation. The other patient was admitted to our clinic with a massive perineal recurrence and metastases to the left groin two years after an abdomino-perineal resection. A wide perineal excision and radical inguinal and femoral block dissection was performed and postoperative 200 K.V. radiation therapy given to each area. This patient has had no further trouble and is well ten years later. The local recurrence in three of these five patients promptly followed inadequate surgical removal and caused two deaths that might readily have been prevented by more radical procedures.

Primary Inoperable Cancer

Eighteen of the 95 patients with primary cancers were unsuitable for operation; eight because of far advanced cancer, and ten for systemic reasons. Nine received 200 K.V. radiation therapy supplemented in one instance by radon seed implantation. Inasmuch as the treatment was given for palliation, the total skin dose exceeded 3000 r in three instances only. Four of these patients died within nine months, another four died after three, three, three and one-half, and four and one-half years respectively, and one is still alive seven years later.

Clinically Operable Cancer

Seventy-seven patients were judged operable. We elected to treat three ultraconservatively. One died of his cancer seven years after local surgical removal. In two instances the tumour was removed with endothermy and the base irradiated, one with radon seed implants, the other with external 200 K.V. radiation. Both are alive at seven and eight years respectively.

*Three other patients have been seen recently in whom cancer recurred in the rectal stump shortly after anterior resection. Restoration of continuity should not be attempted if the growth extends beyond the mucosal structures, and most certainly not if perforation has already taken place.

A radical resection was recommended for 74 patients.

Five refused operation; two had no treatment; three received external roentgen therapy. From the short-term viewpoint they do not appear to have chosen badly. The untreated patients died of their cancer at four and one-half and just over five years respectively. One of those irradiated, aged 76, died of a cerebral hæmorrhage within four months. The other two died of cancer in five and one-half and seven years, respectively.

Nine patients were explored at operation and the lesion found non-resectable; six of these who were closed without benefit of a colostomy ultimately died without obstruction. In three patients with imminent obstruction, a colostomy was performed at exploration. One lived two years; the others died in two weeks and two months respectively.

Resectable Cancer

Sixty resections were performed. Fifteen of these patients were 70 years of age or older. Two were successfully operated upon at 81 years. Fifty of the operations were one-stage abdomino-perineal resections with removal, if need be, of contiguous structures. In three instances anterior segmental resections were performed with immediate end-to-end anastomosis to the ampullary stump. Bacon's operation of procto-sigmoidectomy was carried out on seven. There were no operative deaths in the ten patients who had an ampullary resection or procto-sigmoidectomies. Four of the others, aged 53, 71, 76 and 80 years, died during their hospital stay, from shock and circulatory failure; three of these suffered from hypertension. The hospital mortality for the 60 resections was 6.6%. Three resections were performed in the presence of liver metastases. Of the 53 without known liver involvement who survived operation, 31 were alive five years later (58%); three of these 31 have subsequently died of cancer and one of intercurrent disease.

Although the curability rate with conservative operations has been better than our average—seven of the 10 are still alive—we do not feel that these should supplant abdomino-perineal resection. Properly performed, the latter is a more radical procedure. We have reserved the conservative operations for a carefully selected few. Incontinence has been troublesome in the majority of our procto-sigmoidectomies and if we elect conservatism we presently prefer ampullary resection and primary anastomosis. Anterior resection is suitable for sigmoid cancer and early lesions of the recto-sigmoid, but is not considered adequate for penetrating or perforating cancers. Local mucosal recurrences are relatively common after anterior resection under these circumstances. Neither should continuity be restored in those frequent cases in which potentially malignant satellite polyps exist. Earlier diagnosis will render more patients with mid-rectal cancer suitable for sphincter preservations, but low-lying cancer is best treated by abdomino-perineal resection.

Irradiation

A few very early tumours can be treated perfectly well by external and interstitial irradiation.

Preoperative irradiation preferably with Co^{60} beam therapy is used with benefit, we believe, in approximately one-third of the resections. In many instances the bleeding ceases. Relief from pain and shrinking of the tumour with lessened infection bring about an improvement in the patient's general condition and make the operation technically easier. Occasionally we implant radioactive seeds at operation in a small suspicious residual area of the perineal wound.

Postoperative irradiation is not used unless there is reason to believe that the tumour has been inadequately removed.

Temporary palliation is available without harm to the inoperable patients and those with local recurrence.

CONCLUSIONS

Thirty-five per cent of an unselected group of patients with cancer of the rectum do not receive possible cancericidal treatment because of the presence of advanced recurrent cancer (3%), very advanced primary cancer (17%), inoperability for systemic reasons (10%), or refusal on the part of the patient to accept surgery (5%).

With an absolute five-year survival rate of 40%, cancer of the rectum is still obviously an extremely lethal disease.

The treatment of cancer of the rectum, however, has advanced a great deal in 20 years, from a practically incurable disease, through a stage of low operability (40%) and high mortality (40%), to the present rate of 70% resectability with a hospital mortality of from 3 to 6%.

We now expect a 58% absolute five-year survival in those who survive a curative resection, and nine out of ten of these will still be alive at the end of the tenth year.

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RÉSUMÉ

D'après l'expérience des auteurs, 35% des malades atteints de cancer du rectum ne reçoivent pas le meilleur traitement possible pour une des raisons suivantes: dans 3% des cas la lésion est récidivante, dans 17% elle est très avancée, dans 10% des cas l'opération est contre-indiquée par l'état général du malade et dans 5% des cas le malade refuse de se soumettre à la chirurgie. Si l'on se rappelle que le taux absolu de survie à cinq ans est de 40%, le cancer du rectum doit évidemment être considéré comme une lésion très grave. Des progrès considérables ont cependant été accomplis dans ce domaine depuis 20 ans. Cette affection qui était alors pratiquement incurable a passé par le stage où l'on risquait l'opération dans 40% des cas et où la mortalité atteignait 40% pour en arriver à l'état actuel où en sont les choses: à savoir, un taux de résection de 70% et une mortalité à l'hôpital oscillant entre 3 et 6%. Les chiffres actuels permettent d'espérer une survie de cinq ans à 58% de ceux qui subissent avec succès une résection curative et 90% d'entre eux seront encore en vie 10 ans après l'opération.

CASE REPORT

UNILATERAL RENAL DAMAGE AFTER TRANSLUMBAR AORTOGRAPHY*

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RENAL COMPLICATIONS of translumbar aortography appear to be an important hazard of this valuable diagnostic procedure.[1] We report a case of renal damage secondary to accidental direct injection of 70% sodium acetrizoate (Urokon) into the right renal artery during translumbar aortography.

A 40-year-old white male, auto mechanic, was admitted to the Hôtel-Dieu Hospital of Montreal for the first time on February 13, 1959, for severe hypertension discovered three months before, and non-existent in 1955, when he was investigated in another hospital.

He had been well until the summer of 1958, when he began to notice, without increasing work, that he was easily fatigued. In November 1958, he consulted a physician for slight attacks of exertional dyspnœa, occasional orthopnœa, palpitations and pulsatile occipital and frontal headaches. His systolic blood pressure was 270 mm. Hg. During the two weeks before his admission, he had mild orthopnœa, occasional palpitations and marked pulsatile frontal headaches which awakened him at the end of the night and were alleviated by standing. In spite of rest and rauwolfia medication, his systolic blood pressure remained over 200 mm. Hg.

His family history did not disclose any evidence of hypertensive cardiovascular disease, with the possible exception of the mother, who died at the age of 56. He affirmed that his three brothers and his three sisters were well and normotensive. He had had an infection of the lower urinary tract of unknown origin in 1955, which was symptomatically treated.

On admission, he was a well-developed adult, showing signs of anxiety and stammering. He had fundi that were classified A_2H_1 (after Gans' classification[2]); a systolic murmur grade I/IV, heard along the left border of the sternum in the fourth intercostal space; and blood pressure readings of 230/130 mm. Hg in upright position and 240/130 mm. Hg in recumbent position. The physical examination was otherwise within normal limits.

Blood urea nitrogen value was 50 mg. %, serum creatinine was 1.3 mg. % and serum potassium 4.5 mEq./l. Urine pH was alkaline with a specific gravity of 1.010. There was no proteinuria and the urinary sediment was essentially normal. No catecholamines were detected in the urine by rat bio-assay.[3] Endogenous creatinine clearance value had a mean of 94 ml./min. and the 15-minute excretion rate of phenolsulfonphthalein was 16%.

Teleroentgenography of the heart provided a normal cardiothoracic index. The electrocardiogram showed left ventricular hypertrophy with ischæmic ventricular myocardial lesions of the anterolateral region. An intravenous pyelogram was made on February 17, 1959, using 25 ml. of 50% sodium diacetrizoate (Hypaque). This revealed normal renal structures, except for the fact that the right kidney was 1.25 cm. less in length than the left one.

On the basis of the findings of a severe hypertension recently discovered in a 40-year-old patient with a negative family history of hypertension and a difference in size of kidneys, translumbar aortography was performed to rule out possible occlusive renal artery disease. On February 18, 1959, under general anæsthesia with endotracheal intubation, translumbar aortography was carried out. The aorta was entered successfully on the first attempt with an 18-gauge needle. After prior injection of 26 ml. of 1% procaine, 40 ml. of 70% sodium acetrizoate was injected over five seconds with a pressure injector device (60 lb./square inch*). Femoral arteries were externally compressed by pneumatic cuffs. No scout film was taken during the procedure and no reduction of blood pressure levels was attempted.

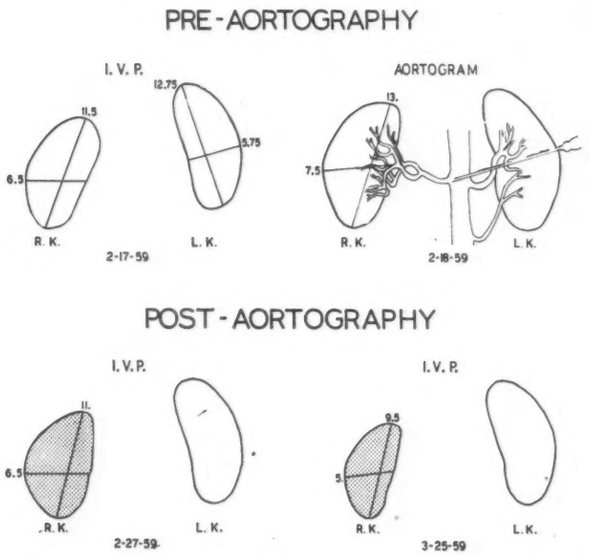

Fig. 1.—Progressive atrophy of right kidney after direct injection of opaque medium into right renal artery.

Radiographic films showed that the tip of the aortograph needle, although in the aorta, was directed towards the origin of the right renal artery and was causing an intense concentration of contrast medium to flow directly into the arterial system of this kidney, with very little in the left kidney (Fig. 1). The distal aorta and the renal arteries were normal except for an aberrant artery to the lower pole of the left kidney. Two films taken at 10 and at 40 minutes after the injection of sodium acetrizoate provided a persistent nephrographic picture of the right kidney alone. No medium was present in the right kidney 17 hours after aortography but the gall bladder and urinary bladder could be well visualized.

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*This device, contrived by one of us (G.E.C.), consists of a double-acting air cylinder which thrusts the plunger of a 100 or 50 ml. syringe, the latter being fixed on a sliding carrier. The oxygen or compressed air which sets the cylinder in motion is equipped with a pressure-reducer in order to keep the latter constant.

Immediately after the procedure, his blood pressure rose to 284/160 mm. Hg, and 30 minutes later the patient complained of a constant sharp pain in the right flank; three hours later the pain was of the boring and sustained type with irradiation to the costovertebral angle. The slightest percussion of these regions enhanced considerably the discomfort of the patient.

Urinary sediments examined at three, four and five hours after aortography revealed hæmaturia of more than 150 red blood cells per high power field and constant proteinuria of one-plus intensity. Six hours after aortography, a right splanchnic block was performed with 25 ml. of 1% procaine. The acute pain subsided completely after 15 minutes. His blood pressure was then 155/110 mm. Hg.

Some degree of pain in the right costovertebral angle persisted till the fourth day after aortography, and an oral temperature of 100° F. for a week during which his blood urea level was 90 mg. % without oliguria. Hæmaturia decreased to five red blood cells per high power field 24 hours after the procedure, and was absent five days later. The proteinuria had a peak of three-plus after six days, but had almost disappeared when the patient was sent home from hospital. On February 27, 1959, serum creatinine value was 2.1 mg. %, endogenous creatinine clearance was 83 ml./minute, and excretion rate of phenol sulfonphthalein after 15 minutes, 8%.

Intravenous pyelograms (Fig. 1) showed a progressive atrophy of the right kidney without evidence of dye excretion on the same side; the left kidney remained normal in size and function.

Six weeks after translumbar aortography, the patient was re-admitted to the hospital. There were no complaints from the patient. Physical examination was the same as on previous admission, and blood pressure in recumbent position was 190/110 mm. Hg. Blood urea level was normal. There was one-plus proteinuria and no microscopic hæmaturia.

A right nephrectomy was performed and at operation an adhesive perinephritic reaction was found. The postoperative period was uneventful. Blood pressure remained elevated (220/140 mm. Hg) in recumbent position, and four days after the surgical intervention, antihypertensive drugs were started. During the nine months after nephrectomy, his blood pressure has been controlled with pempidine (Pempiten) 10-15 mg./day, hydralazine (Apresoline) 150 mg./day, and a purified alkaloidal extract of rauwolfia (Rauwiloid) 6-8 mg./day, with mean levels of blood pressure of 179/98 mm. Hg in recumbent position and 134/76 mm. Hg in upright position.

Pathological Findings

The right kidney was markedly reduced in size (8.5 x 4.75 cm.) but of normal shape (Fig. 2). It weighed only 65 g. The capsule was slightly thickened but stripped with ease except in two small wedge-shaped scarred areas. Surface was smooth and yellowish in colour except for upper and lower poles that were brown-red. The widespread pale yellow area gave the gross impression of a massive zone of infarction. The hilar vessels, arterial and venous, were of normal calibre with a patent lumen. Ureter was normal. The sectioned kidney contained 10 pyramids (Fig. 3), with a cortex measuring only 2 mm. The entire thickness of cortex including renal columns of Bertini were yellow in colour over the whole cut section. The pyramids, by contrast, were red-brown. The pelvic mucosa was smooth, thin and white. Microscopically, numerous sections of kidney showed diffuse structural alterations of the cortex. Large areas were infarcted, only dim outlines of glomeruli and tubules remaining. These widespread areas of coagulation necrosis alternated with a few narrow zones of normal cortex. Numerous foci of ischæmic tubular atrophy were

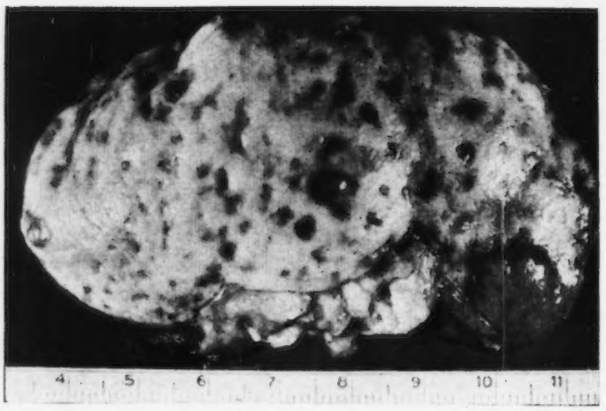

Fig. 2.—Surface of surgically resected right kidney. Note pallor of surface corresponding to diffuse cortical infarction.

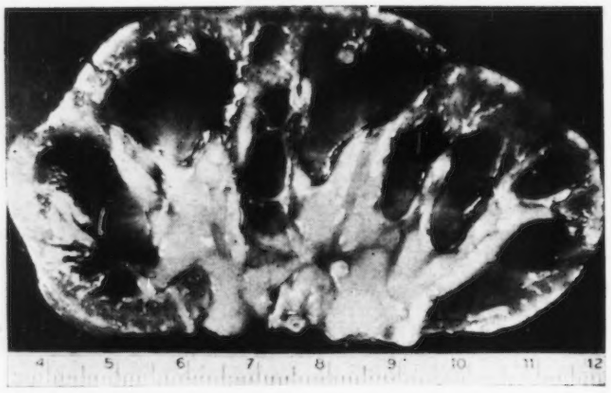

Fig. 3.—Cut section of the right kidney showing diffuse cortical necrosis.

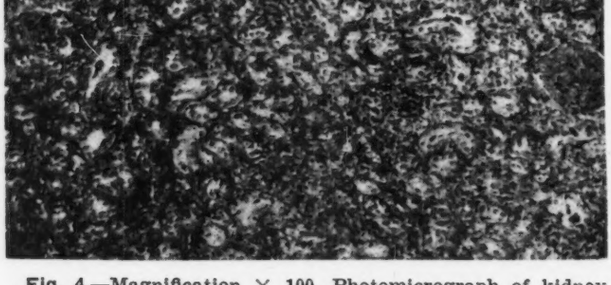

Fig. 4.—Magnification × 100. Photomicrograph of kidney shown in Figs. 2 and 3 removed six weeks after aortography. Note the generalized tubular atrophy and interstitial lymphocytic infiltration.

evident, with clusters of closely approximated glomeruli surrounded by small tubules bordered by pale-staining cuboidal epithelium (Fig. 4). The interstitial tissue in the non-infarcted areas was diffusely infiltrated by lymphocytes.

The arcuate and interlobular arteries showed marked thickening of the intima and media, and considerable narrowing of the lumen. The afferent arterioles were also thickened and hyalinized. In two of eight sections examined, the lumen of two interlobar arteries (Fig. 5) was obliterated by an organized thrombus enclosing multinucleated giant cells in which were found elongated needle-like yellow crystals refractile under polarized light (Fig. 6). A cooled commercial preparation of 70% sodium acetrizoate formed a precipitate which, when examined microscopically under polarized light, consisted of elongated crystals similar to those observed in the thrombosed vessels.

DISCUSSION

An extensive review of the literature[1] reveals the predominance of renal involvement among the complications that follow abdominal aortography. Of these complications unilateral damage almost always occurs after injection of contrast medium directly into the right renal artery. In addition to the 12 cases collected in the literature by Crawford *et al.*[4] to which they added one personal case, we have found descriptions of three other such complications.[5-7]

The distressing aspect of this case was the declaration by the patient's sister, the day after the procedure, that their father, their mother and three sisters were hypertensive!

The technique of translumbar aortography has been performed more than a hundred times since 1943 by the same vascular surgeon (G.E.C.) in our hospital without such complication, using the single-needle technique to enter the aorta just above the origin of the cœliac axis.

Since this unfortunate accident, a preliminary injection of 5 to 8 ml. of dye has been routinely used with a scout film in every subsequent instance to check the position of the needle tip. This precaution is also advocated by other authors.[4, 8, 14]

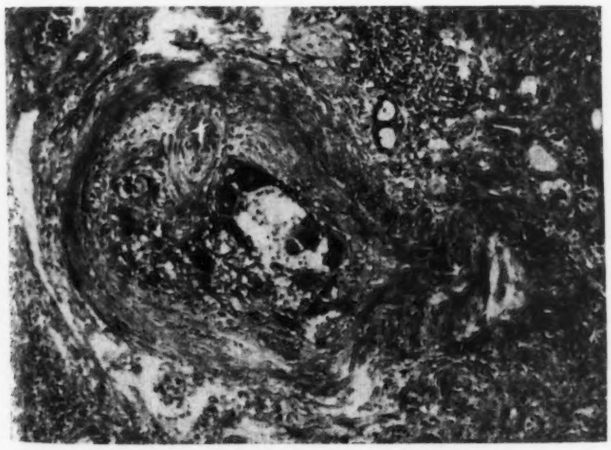

Fig. 5.—Magnification × 100. Thrombosed arcuate artery with foreign-body giant cells.

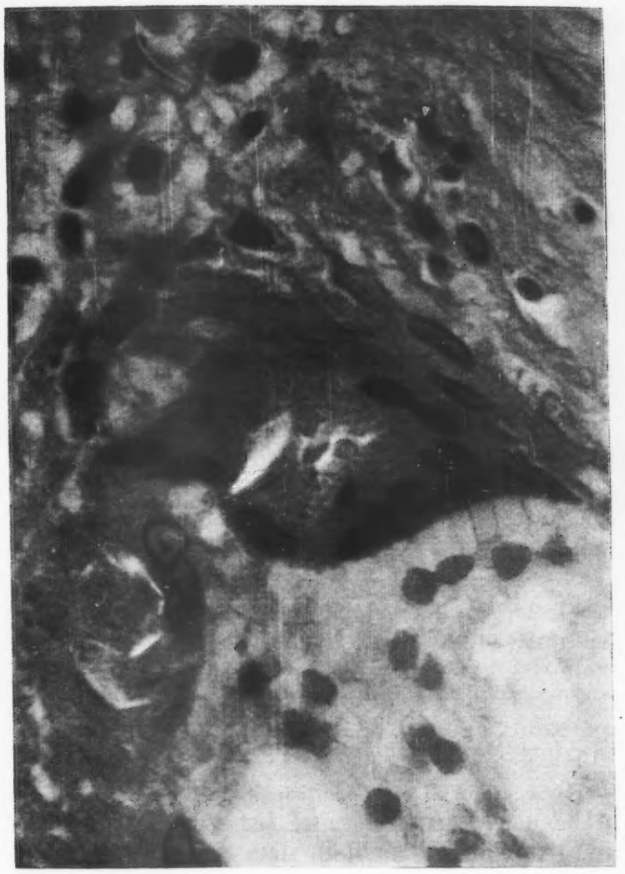

Fig. 6.—Magnification × 970. Needle-like crystal under polarized light in the cytoplasm of the giant cell shown in Fig. 5.

As recently re-emphasized,[9] sodium acetrizoate, although widely used, has definite nephrotoxic and neurotoxic properties. Half the patients who have sustained renal damage after aortography have received sodium acetrizoate. Less toxic radiopaque material is available, and now we frequently use 60% Renographin,® or Vasurix 38,® especially when using the retrograde catheter technique.

Many improvements in technique have been proposed in order to lessen the dangers arising from the use of a potential nephrotoxic dye. Hyperhydration of animals before aortography seems to prevent the toxic renal effect of contrast medium.[10] There is some experimental evidence that 1% procaine injected 60 to 90 seconds before administration of the radiopaque material prevents significant renal injury.[11] Goodwin and Walter[12] used 3-6 ml. of 1% procaine in man to prevent arterial spasm before injecting radiopaque material. Routinely 20 ml. was injected in our patient about two or three minutes before the dye and six additional cubic millilitres immediately before. As Huger, Margolis and Grimson[11] have emphasized, procaine in dogs increases safety, but to equal the dose used satisfactorily in the experimental animal, our patient would have needed 185 ml.

Cases of accidental direct injection of contrast medium into a renal artery resulting in kidney injury have been reported with volumes of from 12

to 100 ml. of 70% sodium acetrizoate. Substantiating it by experimental work on dogs and clinical experience, Beall *et al.*[13] state that renal damage will not result from the use of 30 c.c. or less of 70% sodium acetrizoate if direct renal artery injection is avoided.

Our patient had thigh tourniquets placed over the femoral arteries but they seem to have played an insignificant additive role in the genesis of the renal injury, if we consider with Beall *et al.*[13] that "apparently because of inherent vaso-regulatory mechanisms in the renal circulation, renal blood flow is not increased following aortic occlusion distal to the renal arteries". Of course, when 70% sodium acetrizoate is injected directly into the renal artery, there is no collateral circulation available and the greatest amount of the dye reaches the kidney.

In order to promote a rapid injection (40 ml. in five seconds) of radiopaque material, an oxygen pressure injector apparatus was used. As the volume of dye was delivered directly to the right kidney under high pressure (60 lb./square inch), a certain degree of interstitial extravasation was probably caused, as noted in experimental animals.[14]

Experimental work appears to indicate that ischæmia could be initiated by irritation produced by the contrast medium and that the ischæmic renal tissue is probably more susceptible to injury than a normally vascularized one.[15]

There was no clinical evidence of iodine sensitivity in our patient.

In view of the many complications reported with the translumbar technique of aortography, the actual trend is strongly in favour of the retrograde route by femoral artery catheterization. This procedure is not without risks. Recently, in our hosptial, during investigation of a hypertensive patient, a retrograde femoral artery catheterization was performed by another team. The catheter penetrated the wall and a large sub-intimal dissection of the aorta occurred, followed by immediate severe pain in the abdomen, and 10 minutes later, by a hypertensive crisis (blood pressure over 260/220 mm. Hg), aphasia, left hemiplegia, unconsciousness, external capsular and intraventricular cerebral hæmorrhage. Death occurred eight days after the procedure. Paraplegia occurred after retrograde aortography by femoral artery catheterization in another patient.[16]

The technique of abdominal aortography via either the translumbar or retrograde route must be employed with caution, always keeping in mind that the information to be obtained must exceed the risk involved.

SUMMARY AND CONCLUSION

We have presented and briefly discussed a case of rapid renal atrophy following the injection with a pressure injector apparatus of 40 ml. of 70% sodium acetrizoate directly into the right renal artery. The patient was a 40-year-old man with recently discovered severe hypertension; he was totally unaware of his familial background of hypertension. The need for taking scout films during the intra-aortic injection of a few ml. of radiopaque material to localize the tip of the needle is strongly stressed. Retrograde aortography by femoral artery catheterization also involves serious risks. The favour this procedure actually enjoys should not make the physician forget that the same precautionary measures are necessary.

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Special Article

STANDARDIZATION OF POLLEN EXTRACTS IN CANADA*

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IN CASES of hay fever or bronchial asthma due to pollen allergy, suitable hyposensitization treatment may be expected to produce marked relief of symptoms in 75 to 80% of patients.[1] Some of these successfully treated patients are practically free of symptoms, while others have mild symptoms on a few days of heavy pollination.

Physicians using this form of treatment, however, often obtain inconsistent results. Assuming that a correct diagnosis of pollen allergy has been made, underdosage or overdosage with antigen is responsible for the majority of therapeutic failures. Because sensitivity to pollen antigens varies greatly from patient to patient, the dosage must be carefully adjusted to the degree of sensitivity of the individual as well as to his ability to develop tolerance as treatment progresses. If individual differences are not taken into consideration in planning the dosage schedule, then, more often than

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not, the patient will receive an insufficient amount of antigen or will have frequent constitutional reactions. Either of these situations will lead to poor treatment results.

Incorrect dosage with antigen may be due to one of two reasons: (a) a schedule of hyposensitizing doses that is unsuitable for the individual patient under treatment as discussed above, or (b) the use of pollen extracts which are inadequately standardized. The present study is concerned with the second of these two causes of treatment failure. It is obvious that no matter how skilfully the dosage schedule is adjusted to the sensitivity of the patient, inconsistent results will be obtained if pollen extracts vary in potency between batches. Equally confusing is the situation which occurs when different manufacturers use different numerical units to designate the potency of their extracts.

Therefore, it was decided to investigate the reliability of standardization of pollen extracts in Canada by correlating the various numerical units of potency in use by the manufacturers with the biological activity of the extracts.

There are no previous studies in the literature which correlate the various methods of standardizing pollen extracts with the biological activity of the extracts. Previous discussions of the subject have been concerned almost entirely with the nature of the antigenic fraction.[2-4] As it may be many years before the antigenic fractions in pollen extracts are isolated and characterized, it would be useful to know, for the present, which of the commonly used methods of expressing potency best approximates the biological activity of the extract.

METHODS OF STANDARDIZATION OF POLLEN EXTRACTS

Unfortunately, there is no unanimity of opinion amongst allergists or amongst the manufacturers of allergy extracts as to what constitutes the most satisfactory method of standardizing pollen extracts. There are, at the present time in Canada, at least four different methods of expressing potency of allergy extracts.

1. *Noon Units* (also called pollen units): This unit is based on the weight of pollen used to prepare the extract. One Noon (pollen) unit is equivalent to 0.001 mg. of pollen expressed as Noon (pollen) units per ml.

2. *Weight by Volume Dilution*: This unit is based on weight by volume extraction and dilution. A 1:100 extract contains 0.01 mg. of extracted pollen per ml.

3. *Total Nitrogen Units* (also called pollen units): This unit is based on the total nitrogen content of the finished extract. One total nitrogen (pollen) unit represents 0.00001 mg. of total nitrogen per ml.

4. *Protein Nitrogen Units* (also called Cooke units): This unit is based on the protein nitrogen content of the finished extract. One protein nitrogen unit represents 0.00001 mg. of protein nitrogen per ml.

The Noon (pollen) unit system and the weight by volume dilution system represent different numerical expressions of the same method of standardization. For example, an extract labelled as 1:100 weight by volume dilution is always equivalent to 10,000 Noon (pollen) units. With this exception, it is impossible arithmetically to convert one type of unit into another type. It has been estimated that, for most pollens, 1 protein nitrogen unit is very approximately equivalent to 2 Noon (pollen) units, 2.5 total nitrogen units, or 1:500,000 weight by volume dilution.[5] This approximation is, however, too inexact for clinical use. The vast majority of non-allergists who use pollen extracts are totally unaware of the different methods of standardization. Particularly confusing is the term pollen unit, which is used by one manufacturer to mean a Noon unit and by another to mean a total nitrogen unit.

Extracts standardized in protein nitrogen units are used by the allergy departments of almost all the teaching hospitals in eastern Canada and by the Department of Veterans Affairs hospitals throughout the country. These departments, for the most part, either produce their own extracts or obtain them from other hospital allergy laboratories in Canada and the United States. Weight by volume extracts, usually obtained from commercial suppliers, are used mostly by non-teaching hospitals and private practitioners. The author has no first-hand knowledge of the type of standardization most commonly used in western Canada.

PROCEDURE AND RESULTS

(a) *Standardization of Extracts*

Six ragweed extracts were studied. Three were obtained from hospital allergy clinics that produce their own extracts and three from commercial manufacturers. These extracts were labelled A, B, C, D, E, and F, and their source was not made known to the author until the completion of the investigation. The protein nitrogen content of each extract was determined in the allergy laboratory of the Montreal General Hospital, by a modification of the micro-Kjeldahl method described by Cooke and Stull.[2] The weight by volume dilutions of the extracts were calculated from data supplied by the producers, and the number of Noon (pollen) units were derived from the weight by volume dilution. Total nitrogen values were not determined, as it is difficult to understand how the total nitrogen content of an extract could be a more accurate guide to potency than the protein nitrogen content. The laboratory determination of protein nitrogen is only slightly more complex than the determination of total nitrogen, so that convenience is not a justification for perpetuation of this unit.

The potencies of the six extracts expressed in Noon (pollen) units and protein nitrogen units are compared to a 1:100 weight by volume dilution in Table I. If the conversion factors mentioned in the previous section are approximately correct, then a 1:100 dilution should be equivalent to 10,000 Noon (pollen) units or 5000 protein nitrogen units. Noon (pollen) units are, by definition, derived from weight by volume dilution and the relationship between them will be constant for every extract. However, the assumed ratio of approxi-

TABLE I.—COMPARISON OF UNITS IN SIX RAGWEED EXTRACTS

Extract	*Weight by volume*	*Noon (pollen) units*	*Protein nitrogen units*
A	1–100	10,000	8500
B	1–100	10,000	4500
C	1–100	10,000	2000
D	1–100	10,000	600
E	1–100	10,000	5000
F	1–100	10,000	5500

mately 5000 protein nitrogen units per ml. of a 1:100 dilution is valid for only three extracts. The protein nitrogen content of the other three varies from 600 to 8500 units.

(b) *Comparison of Biological Activity*

If, as has been shown above, there is not a constant relationship between protein nitrogen units and units based on weight by volume determinations, then it seems reasonable to assume that one method is a more accurate measurement of potency than the other. The remainder of the investigation was concerned with determining which method of standardization gives the best correlation with biological activity.

The ability of a pollen extract to evoke a wheal and erythema response in specifically sensitive human skin was used as an indicator of biological activity. Arbesman and Eagle have shown that the most sensitive method of determining skin sensitizing activity is by use of the *in vivo* passive transfer neutralization technique of Cooke and Loveless.[6, 7] This technique is based on the observation that pollen extract in sufficient concentration will neutralize serum from a sensitive individual. When a serum-extract mixture is injected intradermally into a non-sensitive individual, and the site is re-tested with pollen extract 48 hours later, no reaction is obtained. The skin-sensitizing antibody has presumably been bound by the antigen *in vitro* and thus rendered incapable of passively sensitizing the normal skin. Consequently, the minimum amount of pollen extract that suffices to neutralize a given serum is a measure of its antigen content, and the relative activity of any number of extracts can be determined.

For the present study, this technique was modified slightly. A serum obtained from a patient highly sensitive to ragweed pollen and containing a high titre of skin-sensitizing antibody was used throughout the experiment as a source of antibody. In order to measure the neutralizing activity of the pollen extract, 0.2 ml. aliquots of the standard ragweed sensitive serum were mixed in varying dilutions in test tubes with 0.4 ml. quantities of the extracts under study. Mixtures were prepared for each extract with antigen dilutions of 100, 200, 300, 400, 500, 600, 800, and 1000 protein nitrogen units. Sterile precautions were observed throughout. These antigen-antibody mixtures were allowed to stand 24 hours at 4° C., and then heated in a water bath at 37° C. for one hour before the passive transfer.

The passive transfer was carried out by injecting 0.05 ml. of each antigen-antibody mixture intradermally in the back of an individual not allergic to ragweed pollen. After 48 hours, the previously injected sites were challenged with an intradermal injection of 0.025 ml. of 1000 protein nitrogen unit per ml. ragweed pollen extract prepared especially for this purpose. The test sites were inspected in 20 minutes and the reactions graded as positive or negative. Any reaction in which there was a wheal larger than a control injection of ragweed pollen extract alone, and in which the area of erythema extended beyond the borders of the wheal, was considered to be a positive reaction.

A positive reaction on retesting with ragweed extract meant that there was not sufficient antigen in the original antigen-antibody mixture to neutralize completely the skin-sensitizing antibody present in the ragweed sensitive serum. Consequently, the lowest concentration of extract in the antigen-antibody mixture that resulted in a negative skin test on challenge was the neutralizing dose. This experiment was carried out in five different passive transfer recipients. The results are recorded in Table II.

The experiment was designed in such a way that, for each recipient, all six extracts were titrated against the same antibody-containing serum at the same time in the same human skin. The only variables were the extracts themselves, and the differences in sensitivity of the skin of the recipients. The variation in recipient sensitivity is analogous to the individual variation in dose response which occurs in all pharmacological experiments. The results of this type of experiment are usually expressed as the ED_{50} or the amount of drug that will produce the expected response in 50% of test subjects. It was decided to use a similar approach in evaluating our results.

The different neutralization points obtained in different recipients were resolved into a single numerical expression by determining the ND_{50}. This expression represents the dose of ragweed extract which will exactly neutralize a fixed amount (0.2 ml.) of the standard ragweed sensitive serum in 50% of passive transfer recipients. The ND_{50} for each extract was calculated from the data presented in Table II by the use of the formula $\log ND_{50} = x_0 \Sigma \frac{(p_1 + p_2)}{2} d$; whereas x_0 is the lowest dose that will produce neutralization in all recipients, p_1 and p_2 are the proportion of negative skin tests at a given dosage level, and d is the difference between doses producing p_1 and p_2.[8] The ND_{50} for each extract was calculated in protein nitrogen units and then converted to the equivalent weight by volume dilution using the conversion ratios given in Table I.

The ND_{50} represents a response to dosage. In such a situation, the dosage must be increased exponentially in order to produce a linear increase in response, and it is not the sample values but their logarithms that are normally distributed. Therefore, the standard deviation of ND_{50} was calculated from the logarithms of the individual values. The "normal range" represents the mean, plus or minus 1.96 times the standard deviation (5% limits).

Examination of these results shows that there is a much smaller variation in the ND_{50} when the

TABLE II.—NEUTRALIZING ACTIVITY OF RAGWEED POLLEN EXTRACTS

Dose of antigen used in neutralization mixture (P.N.U./ml.)	*Number of negative reactions on retest in five recipients**					
	Extract A	*Extract B*	*Extract C*	*Extract D*	*Extract E*	*Extract F*
1000	5	5	5	5	5	5
800	4	4	5	5	4	5
600	4	3	5	5	3	5
500	2	4	4	4	1	4
400	2	1	2	3	0	2
300	1	1	0	2	0	1
200	1	0	1	0	0	0
100	0	0	0	0	0	0
ND_{50} (P.N. units/ml.)	574	584	463	410	743	462
"normal range"	364 to 828 protein nitrogen units					
ND_{50} (weight by volume)	1:1480	1:770	1:440	1:150	1:1600	1:1210
"normal range"	1:125 to 1:3161 weight by volume dilution					

*A negative test indicates neutralization of antibody.

extracts are standardized in protein nitrogen units than when they are standardized on a weight by volume dilution basis. In 95% of passive transfer subjects the ND_{50} will fall between 364 and 828 protein nitrogen units, with the ratio of the upper limit of the normal range to the lower limit being 828/364 or 2.3. When weight by volume dilutions are used to standardize the extracts, the upper and lower limits are 1:3161 and 1:125, with an upper to lower level ratio of 25.3. Thus, the normal range of the ND_{50} shows 11 (25.3/2.3) times greater variation for extracts standardized by weight by volume dilution methods than for extracts standardized in protein nitrogen units.

DISCUSSION

The results obtained in this study indicate that the possible variation in biological activity of ragweed pollen extracts standardized by weight by volume dilution methods is 11 times greater than for protein nitrogen unit standardization. Although no completely satisfactory method of standardizing pollen extracts is likely to be found until the antigenic fractions are chemically isolated, it would appear that standardization in protein nitrogen units is the most reliable method, currently available, of measuring potency for clinical purposes.

These conclusions are, by the nature of the experiment, purely empirical and do not imply that the antigen of ragweed pollen is necessarily a protein. There does, however, seem to be a good correlation between protein content and biological activity. It is not surprising that weight by volume methods of standardization yield extracts of variable potency because the antigenicity of crude ragweed pollen is determined by a large number of factors including the date of collection, soil, and climatic and geographical conditions. No scientifically trained person would assay gold by weighing the crude ore before smelting, yet this very principle is often applied to the assay of a highly potent and variable substance used in the treatment of human disease. A small error in the dosage of ragweed pollen extract may result in a severe constitutional reaction. Nevertheless, many pollen extracts are amongst the crudest preparations used in modern medicine.

The use of four different methods of assaying pollen extracts in Canada leads to endless confusion, and in many cases, poor results in the treatment of pollen allergy. A similar situation exists in the United States, where the confusion is compounded by the larger number of manufacturers of pollen extracts.

The American Academy of Allergy in conjunction with the National Advisory Allergy and Infectious Disease Council has organized a committee to investigate the problem of standards. The approach of this committee has been that no progress can be made until the nature of the allergen is established, and that the entire effort of the committee members should be directed towards this end.

This approach, while laudable from a scientific point of view, is not consistent with the usual practice in other branches of pharmacology. For instance, digitalis leaf (also a botanical preparation) was adequately standardized for many years before the nature of the cardiac glycosides was understood. The method used for assaying digitalis preparations is only remotely related to the therapeutic action of the drug, and yet it is perfectly satisfactory for clinical purposes. Arbitrary standards are better than no standards. If the allergen in pollen extracts is discovered, then this material can then be standardized on a simple weight basis. However, it has taken years to elucidate the nature of the cardiac glycosides, and there is no reason to suppose that the task will be any less complex for pollen antigens.

Further delay in developing a uniform method of standardization, no matter how imperfect it may be, can only lead to increasing misunderstanding amongst Canadian physicians who treat pollen allergies. It is therefore suggested that if protein nitrogen determination gives the best correlation with biological activity, this unit of standardization should be adopted by all manufacturers of allergy extracts in Canada.

SUMMARY

Four different methods of standardizing pollen extracts are in common use in Canada. This study has shown that standardization in protein nitrogen units is, at the present time, the most reliable method of estimating the biological activity of ragweed pollen extracts. The adoption of protein nitrogen standard-

ization by all producers of pollen extracts in Canada would lead to more satisfactory and consistent results in the injection treatment of pollen allergies.

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SHORT COMMUNICATION

THE RATIO TOTAL SERUM CHOLESTEROL/(PERCENT ALPHA LIPOPROTEIN)–2 AS A MEANS OF SEPARATING GROUPS OF CORONARY FROM NON-CORONARY SUBJECTS*

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CLAUDE ALLARD, Ph.D., *Montreal*

THERE IS considerable evidence that patients suffering from coronary atherosclerosis tend as a group toward hypercholesterolæmia.[1] This disease is also generally associated with an increase in the beta lipoprotein and a decrease in the alpha lipoprotein levels in the serum.[2]

The purpose of the present investigation was to evaluate again the changes in serum cholesterol and lipoprotein levels in the hope of finding a better way to differentiate coronary from non-coronary subjects.

The data were compiled from case records of patients admitted to hospital between November 1958 and November 1959 in whom both the serum cholesterol and lipoprotein levels were determined during or after their stay in hospital. Patients suffering from thyroid or ovarian disturbances, diabetes, or marked obesity were excluded from this study. Patients whose blood analyses were carried out during or after any dietary or medicinal treatment which might have modified their serum lipid pattern were also excluded. The remaining subjects were then carefully evaluated and classified into "coronary" and "control" groups. The "coronary" group included subjects who had suffered a proven myocardial infarction or presented definite clinical evidence of coronary insufficiency. The "control" group included subjects completely free from any clinical manifestations of coronary disease. The mean age of the 29 "coronary" patients was 44 years and the group included 22 males between 33 and 52 years and seven females between 37 and 52. The mean age of the 38 "control" subjects was 32 years, and these included 31 females from 7 to 57 years and 7 males from 12 to 37.

Blood samples were taken in the fasting state. A clot was allowed to form at room temperature and the serum collected after centrifugation. Determinations of both the total cholesterol and lipoproteins were carried out. Cholesterol analyses were performed as described by Schoenheimer and Sperry[3] and the serum lipoproteins by electrophoresis. This was carried out on thick filter paper (Schleicher and Schuell No. 2230), using 1 ml. of serum previously stained with 0.1 ml. of 1% acetylated Sudan Black B solution in acetone.[5] Veronal buffer, 0.075 ionic strength, pH 8.6, was used. The strips were fixed in horizontal plastic frames which were placed in closed compartments. Conditions were allowed to equilibrate for 30 minutes, then electrophoresis was carried out for 16 hours at 6 volts/cm. (250 volts, 50 milliamperes). The paper strips were then dried over gentle heat. To determine the percentage of the serum lipoproteins the point of origin was discarded, and each fraction separated by electrophoresis was cut into small pieces and extracted in 95% ethanol-ether (3:1) for 24 hours at room temperature. These pieces were then washed with alcohol-ether until no colour remained. The washings were added to the original extract and made up to a standard volume. The optical density of the extracted Sudan Black was read in a Coleman spectrophotometer 6 C at 680 mμ and the results were calculated as a percentage of the total Sudan Black, by reference to a previously prepared standard curve.

The results of the present study have been summarized in Fig. 1. The total serum cholesterol values and the percentage of alpha lipoproteins or "percent alpha" were plotted individually. There was an overlapping between the "control" and the "coronary" groups with regard to both of these parameters although it was less pronounced with the "percent alpha". This fact prompted us to calculate various mathematical combinations with these two lipid values in order to emphasize the "percent alpha" parameter. When the total serum cholesterol was divided by the square of "percent alpha", a more clear-cut separation between the two groups was observed (Fig. 1).

Classical methods of statistical analysis such as the Student's "t" test could not be applied for these ratio values because the form and property of the

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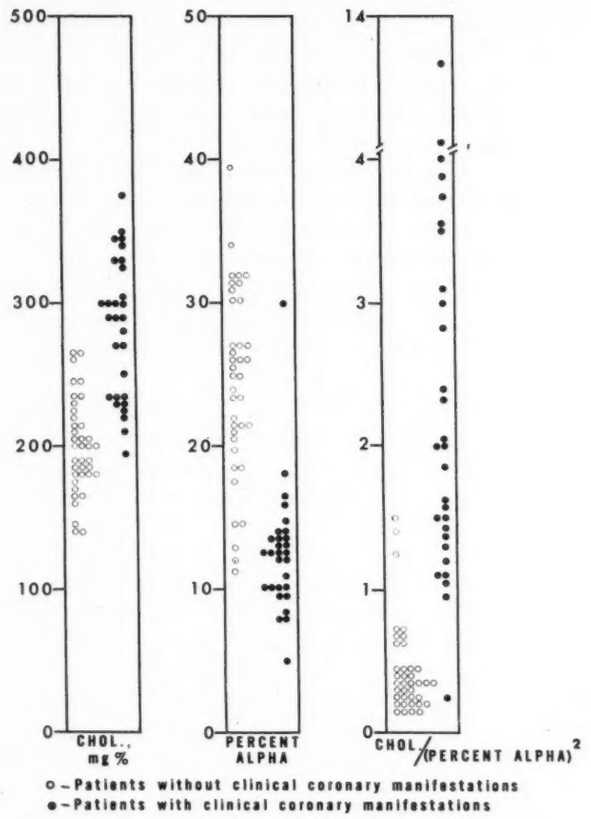

Fig. 1.—A comparison of the concentration of total cholesterol and percentage of alpha lipoproteins (percent alpha) in blood serum and the ratio of total cholesterol/(percent alpha)² in coronary and non-coronary subjects.

distribution curve were unknown. Using the chi-square criterion and choosing after examination of the results an *arbitrary value* of 0.8 as an index, the statistical analysis revealed that the difference in the distribution was significant at a probability level of less than 0.0005. It has to noted, however, that this probability value should be considered with caution since it was established after the introduction of a subjective criterion to separate a given number of values.

It has to be emphasized that the "control" and "coronary" subjects were not matched either by age or sex and that the number of values was small. The conclusions therefore are tentative, but we are encouraged to proceed on a larger scale to test the validity of the ratio of total serum cholesterol to the "percent alpha" squared as a biochemical characteristic of coronary atherosclerotic patients.

The authors wish to thank Dr. Hymie Gordon, Cape Town, South Africa, for his helpful criticism of the manuscript. The support and encouragement of Dr. Paul David, Director, Montreal Institute of Cardiology, has been greatly appreciated. The collaboration of Drs. Joseph Sternberg and Enid Pascoe-Dawson in carrying out the blood analyses is acknowledged. Our thanks are extended to Misses Colette Drouin-Naud and Denise Plante for their help in compiling the data. We are also indebted to the medical staff of the Institute of Cardiology and of Maisonneuve Hospital for permission to study the case record of their patients. Dr. Jacques St-Pierre, Director, Department of Statistics, University of Montreal, was responsible for the statistical analysis of the data.

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(Information regarding contributions and advertising will be found on the second page following the reading material.)

THE B.M.A. REVIEWS THE ROYAL COMMISSION'S REPORT

The Representative Body of the B.M.A. met on May 19 to consider the recommendations of the B.M.A. Council regarding the report of the Royal Commission on the Remuneration of Doctors and Dentists in Britain's National Health Service. The Minister of Health had announced in Parliament, and further elaborated in a letter to the B.M.A., that the Government was prepared to accept the recommendations contained in the majority report, *in toto*, provided that the profession, too, would accept these recommendations as a "package deal".

The B.M.A. Council made the following recommendations to the Representative Body:

1. That the offer of the Minister as made in his statement to Parliament and as amplified by his letter of April 5, be accepted.
2. That the Minister's invitation to enter into detailed discussions by means of Joint Working Parties be accepted without delay.
3. That the outcome of these discussions be reported to the Representative Body for consideration after Divisions have had time to discuss these issues and instruct their representatives thereon.

After much discussion the Representative Body accepted Council's recommendations.

The Commission had recommended increases in remuneration averaging 24% (the profession had claimed 29%), changes in the method of calculating the pool from which general practitioners are paid—generally speaking to the advantage of the profession—and the creation of a Review Body consisting of seven independent persons of eminence and experience to advise the Prime Minister on matters of remuneration.

Discussion by the Representative Body indicated that while some members of the profession regretted that the increase in remuneration did not meet the Association's request, most were prepared to accept the result. Some discussion arose on an amendment seeking fee-for-service payments for an increased list of services (now restricted to maternity services). However, the amendment, which was linked to another suggesting a reduction in the maximum lists with a corresponding increase in the capitation fee, was lost.

Most of the discussion centred about the appointment of the Review Body. As proposed, it would sit in judgment of competing claims and submit recommendations to the Prime Minister. The profession would not have direct access to the Review Body but its submissions would be presented to Government, who would in turn submit them to the Review Body.

Terms of reference for the Review Body have not been specifically set out, and some concern was expressed that one should not accept the Minister's proposal until such time as satisfactory arrangements have been agreed upon for the functioning of the Review Body. Unfortunately this suggestion nullified the Minister's proposal for blanket approval and was lost.

It was evident that the profession wishes the Review Body to make recommendations on financial arrangements alone. A suggestion contained in the minority report that it be responsible for broad strategic planning in the N.H.S. was unacceptable.

It is obvious from a record of the discussion that the profession disagreed with some of the recommendations which the Royal Commission had proposed. It was, however, equally obvious that the Government could not be pleased with many of the recommendations which they had now pledged to accept. Thus the device of a "package deal" acceptance effected a compromise between the profession and government, with most of the gains to the profession's advantage.

Editorial Comments

CARCINOGENIC EFFECTS OF THERAPEUTIC AGENTS

From time to time publications appear in the medical press that report the results of experimental work carried out in the laboratory. The impression is gained that the authors of these articles are of the opinion that the individual reader has a wide background knowledge of the subject under discussion. In practice, we know that few clinicians have a comprehensive understanding of such laboratory experiments. It is therefore inevitable that a great deal of confusion must frequently result from many of these published findings. This state of affairs is perhaps best exemplified in the distorted conclusions which may well be drawn from animal experimentation in the complex field of cancer research.

Some substances which are generally considered to be innocuous or safe to administer in therapeutic doses have been found under the conditions of laboratory study and investigation to have a carcinogenic effect in some species of experimental

animals. Because of the lack of critical appraisal of these experiments, anxiety is often produced in the minds of clinicians who attempt to apply these findings in practice.

When the subject of malignant disease is being dealt with, the emotional factors involved often blunt critical faculties. The need for perspective in the evaluation of experimental data in animals and their relationship to cancer in humans is long overdue. Many drugs which have found widespread acceptance in clinical medicine and are extremely valuable therapeutic agents have been shown to produce a carcinogenic effect under certain laboratory conditions. An example is the intramuscular iron-dextran complex which has been used successfully for more than six years in the treatment of iron deficiency. It has been proved to be an extremely valuable drug and some 100 publications in the medical and scientific press confirm its value.

Three years age, Richmond[1] reported the induction of sarcoma in rats which had received massive doses of iron-dextran complex in the same site over a long period. This work was extended by Haddow and Horning[2] who, using similar massive overloading doses of iron, succeeded in producing a high yield of tumours in rats and mice. Widespread publicity surrounded this work as the result of a leading article in the *British Medical Journal*.[3] The effects of massive iron overloading with iron-dextran complex have also been studied in the guinea pig and rabbit, but even under similar experimental conditions sarcoma could not be induced. Eighty-two hamsters also received swamping doses of iron-dextran, but only one sarcoma appeared.

Golberg,[4] another authority in this field, has shown that the absorptive mechanisms in the rat and mouse differ from those in other animals, thus demonstrating the importance of species variation in work of this kind. It is pertinent to observe that although millions of patients have been successfully treated for iron deficiency with iron-dextran complex over a six-year period, no tumours in man have been reported.

This recent work must not be viewed in isolation, for many therapeutic agents in common use, including œstradiol, stilbœstrol, progesterone, testosterone, desoxycorticosterone, urethane and sulfanilamide, have also been shown under experimental conditions to produce sarcoma at the site of injection or implantation. Moreover, of the so-called "innocuous" substances which have been shown to be carcinogenic in rats and mice, sodium chloride, glucose, fructose, galactose and lactic acid are included.

In contrast to these findings with therapeutic agents, Szepsenwol[5] reported a high yield of tumours in 16 mice who were maintained from the age of three months on a diet supplemented with hard-boiled eggs, one or two daily. Sixteen other mice from the same litters were kept as controls and maintained on the same diet but without eggs. Of the control group only two animals developed tumours, but of the 16 experimental mice no fewer than 12 developed malignant tumours. It is not suggested that as a result of this work eggs should not be ingested by man.

It would appear that the clinical risk involved in the use of drugs that have been shown to produce carcinogenic effects in animals is hypothetical and requires to be balanced against the therapeutic needs of the patient. T. H. C. BARCLAY

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DIFFICULTIES IN PSYCHOPHARMACOLOGICAL RESEARCH

Research in the field of pharmacological agents which act on the psyche, scanty and poorly developed throughout decades while pharmacological research was flourishing in other fields, has come to the foreground of scientific and practical interest with the advent and widespread use of tranquillizers and antidepressant drugs. However, research in this particular field encounters specific difficulties, mainly because of the lack of a working theory relating biochemical or pharmacological events to behaviour. By and large, psychopharmacology is concerned with the action of drugs on complex behaviour, i.e. on mood, emotions, communication, learning, etc. On the other hand, it investigates their action on substances like serotonin, and on electrical potentials in the brain. There is no single theory enabling the researcher to integrate the behavioural data with biophysiological knowledge.

Callaway and Stone[1] of the Langley Porter Neuropsychiatric Institute in San Francisco have critically reviewed the existing psychopharmacological theories that are not entirely successful yet stimulating and containing the core for future research. The theories suggested by the hallucinogens or psychotomimetic substances have failed to prove these to be useful models for testing antipsychosis drugs. However, studies based on the body-image approach, the galvanic skin response pattern, the sensory-tonic field theory, all of which are concerned with more subtle changes induced by the hallucinogens, allow the collection of repeatable data. From many controlled studies it is apparent that there are drugs which influence emotions and mood. But clinical descriptions of these changes leave much to be desired. The self-rating technique devised by Wendt, consisting of 100-200 adjectives to which a subject has to respond rapidly under the influence of drugs, seems to promise an objective approach to problems of subjective reactions.

Studies concerned with the physiological changes accompanying emotions are important, although they offer some difficulties. No doubt a drug may influence the emotion and this in turn may influence bodily functions. But the drug may also influence directly the physiological change under study, or it may modify the effect of emotion on the bodily change without modifying the emotion itself. Another set of studies is concerned with the effect

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of drugs and test performance disrupted by introducing stressful or anxiety-provoking factors into the test situation. However, in evaluating the objective measures of performance one must not overlook the fact that they are no less subject to social and environmental effects than are the subjective or introspective reports of a subject.

Much work is yet to be done in the field of studying the effects of drugs on instrumental responses serving the purpose to avoid shock, as compared with the unconditioned components of the response. Eysenck's theory based on competing cortical excitatory and inhibitory potentials, related to extroversion and introversion, and in turn to the effects of stimulant and depressant drugs, may be of great heuristic value but is still far from showing the royal road to a comprehensive psychopharmacological theory. Finally, theories based on viewing the human mind as a data-processing computer may yield valuable information and are being developed. Despite all these difficulties, research in psychopharmacology appears promising and should be heartily encouraged.

M. TYNDEL

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PLANNING THE FUTURE IN MEDICAL PRACTICE

Graduates in medicine are often entirely ignorant of the activities of practising doctors in the world at large outside the medical schools. In Australia for the past two years representatives of the College of General Practitioners, in an effort to remedy this ignorance, have invited junior hospital medical staff personnel, especially those in the pre-registration year of hospital residence, to meet in an informal way in order to discuss topics of planning that are of interest to the doctor at this stage in his career (*M. J. Australia*, 1: 470, 1960).

In selecting the panel of representatives, the emphasis has been kept as far as possible on youth, partly because it was felt that the presence of too many elder statesmen of the profession might inhibit free discussion, and partly because the residents themselves requested it. They wanted to hear how the problem of entry into practice had been faced by men of their own generation, rather than by men perhaps a quarter of a century before them.

Educational topics—studies at home and abroad, scholarships, postgraduate education for general and specialty practice—were discussed. Professional topics included careers in medicine, general practice ("locums", partnerships, book-keeping) and ancillary medical services. Finally, the economics of private practice were studied—cost of home, car and essentials; insurance, education of their children; middle life, later life, and planning for retirement.

The College is aware that the results of these meetings can not be fully evaluated until they have been held for several more years. Some of the conclusions reached in the discussions are similar to those that have been reached by medical educators in Canada.

It was noted that a foreboding of lowered socio-economic status in general practice, should the medical profession be "nationalized" after the British pattern, was common to most of the young graduates. The College decided that political indoctrination should not be a function of these meetings, and as far as possible the political aspects of medical practice were avoided.

One suggestion that received considerable argument and discussion was that, in the second-year roster, the doctor preparing for a specialist career spend a period of three months as a *locum tenens* or assistant in a general practice. It would probably provide him with his only experience of general practice.

This experiment in medical education at the graduate level on the theme of planning the future in medical practice would appear to be one that would be well received by young doctors in Canada.

THE STEINER THERAPY OF DISSEMINATED SCLEROSIS

The Swiss Association for Multiple Sclerosis held a meeting of its Medical Council in the form of a round-table conference in order to discuss among other things the claims by G. Steiner of Detroit, U.S.A., that multiple sclerosis is due to spirochætal infection and to review his claim of the efficacy of his triple therapy. A factual and objective discussion, in which all those present were given an opportunity to relate their personal experience with the "triple therapy", took place, and not one claimed any marked results from this treatment. In no case were the reported results any better than could be anticipated in the natural course of the disease. It was also brought to the notice of the participants that Steiner himself has not given any generally available report on the 650 or more patients he is supposed to have treated for the last five years.

A warning against uncritical reports of cures of multiple sclerosis was issued. The treatment was rejected by all those present who were treating patients with disseminated sclerosis.

The presence of spirochætes in the brain and spinal cord as well as spinal fluid of patients with disseminated sclerosis was considered not to have been proven in any definite manner. After the suggestion of serologists who were present in an advisory capacity, it was decided to initiate a systematic investigation of Steiner's hypothesis by serological means.—*Schweiz. Arztezeitung*, 41: 123, 1960.

W. GROBIN

Medical News in brief

THE PROBLEM OF DISTENSION IN LOW SMALL INTESTINAL OBSTRUCTION

The effects of distension of ileum and jejunum in low small bowel obstruction are more baneful than all the other deleterious components of the syndrome. The rise in intraluminal pressure, compression of veins, œdema of the wall and increased secretion set up a vicious circle leading to anoxia, fatigue, perforation, mucosal ulcers and absorption of toxic material. In such a state, the condition of the patient is grave even if the obstruction is relieved.

Gastro-intestinal intubation and decompression was a great advance in treatment, but the surgeon was lulled into a false sense of security so that operation was delayed, sometimes fatally. At operation distension is a problem with which it is hard to deal without the danger of peritoneal contamination, damage to the bowel wall, incomplete emptying and the loss of a great deal of time.

A method of decompression using a modified Pool's sucker end 27.5 cm. long with 2 mm. perforations is described by Shar (*Brit. J. Surg.*, 47: 216, 1959). It is inserted into the distended bowel five feet above the obstruction, the proximal intestine being emptied first and then the bowel between the sucker and the obstruction emptied. The technique avoids contamination and the instrument does not get plugged.

With successful decompression of the small intestine, the manipulations necessary to find and correct the obstructing lesion are less dangerous and the post-operative ileus is decompressed in less than 48 hours.

CATHETERIZATION AS A MEANS OF DIAGNOSING LATENT PYELONEPHRITIS

Careful urinary culture studies are stressed by all in order to uncover latent and unrecognized cases of pyelonephritis. Plattner *et al.* (*Schweiz. med. Wchnschr.*, 90: 282, 1960) found that unless one resorted to catheterization in women it was impossible to obtain non-contaminated specimens. The recently expressed opinion of various writers that 3% to 10% of catheterizations produce infection of the urinary tract has been a cause of serious concern and it was decided to investigate the degree of this danger. At intervals of one to two days 109 catheterizations were carried out in 30 women. None of these women showed any bacteriura at the time of the next catheterization, and of the five who had bacteriuria initially, none had an increase in the content of micro-organisms or the appearance of any new ones—this in spite of the fact that in 58 cases the catheter was found to contain micro-organisms by culture.

It is concluded that catheterization carried out under proper precautions does not cause contamination of the bladder nor does it aggravate pre-existing bacteriuria. Catheterization should not be used as a routine, but it is the best way of collecting urinary samples for bacteriological investigation.

LIMITATIONS OF VAGINAL DOUCHING

Vaginal douching is probably one of the oldest forms of gynæcological treatment; it is an example of a method of treatment, the indications for which decrease as knowledge increases. For centuries douching has traditionally been used for cleansing of the vagina and in many countries it is still a common practice. But, in fact, the healthy vagina possesses a most efficient defence mechanism and douching is never necessary for women in normal health.

Douching for the purpose of cleansing is essential in patients in whom certain types of pessary are used, particularly rubber ring pessaries. Many gynæcologists are now using rings made of plastic for the treatment of prolapse. Plastic rings do not cause offensive discharge and one of their great advantages is that douching can be dispensed with entirely or used only infrequently. In the treatment of vaginal infections, douching is a relatively ineffective method—the solution used is too dilute and its effect too evanescent, whereas a prolonged effect can be obtained by chemicals inserted into the vagina. Use of warm douches is often recommended in the treatment of chronic salpingitis.

The safest method of administering a vaginal douche is by means of a douche can with a rubber tube and vaginal nozzle. The solution is poured into the vagina by the force of gravity. Methods that would permit use of excessive pressure may force the solution into the uterine cavity.

Traumatic injury to the vaginal wall may occur if excessive force is used in inserting the nozzle. Scalds may be incurred by the use of too hot a solution. Strong solutions of antiseptics may set up a chemical vaginitis. It is wisest, on the whole, to restrict vaginal douching to the use of plain water or of physiological solutions such as lactic acid, vinegar or saline or to sodium bicarbonate where indicated.

Pregnant women should never douche. Especially dangerous is the use of a syringe. Air may be forced into the uterine blood vessels with consequent fatal air embolism. Embolism with soap or disinfectant solutions may lead to intravascular hæmolysis, also with fatal consequences. — Josephine Barnes, *The Practitioner*, 184: 668, 1960.

ECHINOCOCCUS OF THE LUNGS

Sixty-two patients with echinococcus of the lungs were observed by Askerkhanov in Dagestan (U.S.S.R.) during the past five years (*Khirurgiya*, 1: 31, 1960). Echinococcosis is endemic in Dagestan and is found in some 5% of all surgical hospital patients. Forty per cent are found to have the disease in the lung and 45% in the liver. Diagnostic difficulties may require diagnostic pneumothorax, pneumoperitoneum and pneumomediastinography. Early operation with radical excision of the cysts is recommended. It was carried out on 52 of the 62 patients.

Astrozhnikov reports on 26 patients with pulmonary echinococcosis of whom 21 underwent operation (*Ibid.*, 1: 37, 1960). They constituted 21% of all 124 patients with echinococcosis. Astrozkhnikov draws attention to the increased diagnosis of pulmonary involvement in echinococcosis and attributes it to improved diagnosis of chest disease. He believes that the danger of secondary dissemination of echinococcus through break of the cyst capsule has been exaggerated in the past, as the majority of echinococcus cysts are sterile.

(Continued on advertising page 16)

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NEW DRUGS

This listing of new products is based on information received from Dean F. N. Hughes, Faculty of Pharmacy, University of Toronto, and the *Canadian Pharmaceutical Journal*, to whom we owe thanks.

ANTIBIOTIC

Chloramphenicol: CHLOROTINE (Pr), Maney

Description.—Capsules of 250 mg.
Indications.—Infections due to organisms sensitive to chloramphenicol.
Administration.—Usual dosage, 1 capsule 4 times daily.
How supplied.—Bottles of 16 and 100.

ANTICOAGULANT

Warfarin sodium: PANWARFIN (Pr), Abbott

Description.—Each grooved tablet contains warfarin sodium [3-(alpha-acetonylbenzyl)-4-hydroxycoumarin sodium] 5 mg., 10 mg. or 25 mg.
Indications.—Treatment and prophylaxis of intravascular thrombosis and embolism, including myocardial infarction, postoperative thrombophlebitis, etc.
Administration.—As a general guide, about 50 mg. is a satisfactory initial dose and about 10 mg. is usually sufficient to maintain therapeutic prothrombin levels.
Warning: Constant supervision of patient is essential, daily prothrombin determinations being made to control dosage.
How supplied.—Bottles of 100 and 1000.

ANTIHISTAMINICS

Tripolidine and pseudo-ephedrine: ACTIFED, B. W. & Co.

Description.—Each tablet *or* 10 c.c. (2 teaspoonfuls) of syrup contains: Actidil (tripolidine HCl) 2.5 mg. and Sudafed (pseudo-ephedrine HCl) 60 mg.
Indications.—Prophylaxis and treatment of respiratory congestion and allergic symptoms, e.g., hay fever, common cold, allergic asthma, sinusitis.
Administration.—Usual dose, 2 teaspoonfuls of syrup or 1 tablet 3 or 4 times daily. Children, up to 6 years of age, ½ adult dose.
How supplied.—Tablets, bottles of 100 and 500; Syrup, bottles of 16 and 80 fl. oz.

Dextro-brompheniramine maleate: DISOMER Chronotabs, Syrup, White

Description.—Each *Disomer Chronotab* contains 6 mg. dextro-brompheniramine maleate, equally divided between the outer layer for prompt effect and the inner core for release 4 to 6 hours after ingestion. Each 5 c.c. teaspoonful of *Disomer Syrup* contains 2 mg. of dextro-brompheniramine maleate in a flavoured black currant syrup.
Indications.—Symptomatic management of allergic states responsive to oral antihistamines, hay fever, vasomotor rhinitis, atopic and contact dermatitis, drug and serum reactions, urticaria, non-specific pruritus, food allergy, and certain cases of bronchial asthma.
How supplied.—Chronotabs, bottles of 100; Syrup, bottles of 16 fl. oz.

ANTIHYPERTENSIVES

Guanethidine: ISMELIN, Ciba

Description.—Guanethidine, antihypertensive agent requiring once-daily dosage, exerts a selective inhibitory effect on the sympathetic nervous system.
Indications.—All types of hypertension, especially in moderate and severe cases. *Contraindicated* in the presence of phæochromocytoma.
Administration.—Because of gradual onset of effect and prolonged action, initial dosage should be small and increased gradually as follows: one 10-mg. tablet daily for the first week. A few patients will respond to this low dosage; others should be given two 10-mg. tablets in one dose for the second week. Subsequent increments of dosage should not be more than 10 mg. daily, with intervals of one week at each dosage level.
The majority of patients will respond to 30-60 mg. daily. If necessary, the dose may be increased as above to 100 mg., or, in rare cases, to 150 mg. daily.
Side effects.—Characteristic of sympathetic inhibitors—orthostatic hypotension, diarrhœa, etc.
How supplied.—Tablets of 10 mg. (pale yellow, scored) and 25 mg. (white, scored); bottles of 100 and 500.

Hydrochlorothiazide and deserpidine: ORETICYL (Pr), ORETICYL FORTE (Pr), Abbott

Description.—*Oreticyl 25*: Each grooved tablet contains: Oretic (hydrochlorothiazide) 25 mg., Harmonyl (deserpidine) 0.125 mg.
Greticyl 50: Oretic 50 mg., Harmonyl 0.125 mg.
Oreticyl Forte: Oretic 25 mg., Harmonyl 0.250 mg.
Indications.—Hypertension.
Administration.—1 to 4 tablets daily, usually starting with 1 tablet 3 times daily and adjusting. "Forte" recommended at commencement of treatment.
How supplied.—Bottles of 100 and 1000.

Hydrochlorothiazide-reserpine-butabarbital: TENED-Bitab (Pr), Can. Pharm.

Description.—Each two-toned purple dappled tablet contains: hydrochlorothiazide 50.0 mg., reserpine 0.5 mg., butabarbital 30.0 mg.
Indications.—For the treatment of essential hypertension through the reduction of blood pressure, relief of tension and anxiety, elimination of excess fluid.
Administration.—1 each morning for 5 days—stop medication for 2 days and then repeat. For severe diastolic hypertension suggested dosage is 2 tablets daily.
Caution: The withdrawal period of 2 days should enable the patient to regain any potassium depletion; however, a potassium supplement may be indicated in some cases.
How supplied.—Bottles of 50, 500, 1000. .

APPETITE SUPPRESSANTS

Phendimetrazine bitartrate: PLEGINE, Ayerst

Description.—Each scored tablet contains 35 mg. phendimetrazine bitartrate.
Indications.—For the suppression of appetite in the obese patient.
Administration.—1 tablet 2 or 3 times daily, 1 hour before meals.
How supplied.—Bottles of 60 and 500.

Amphetamines: OBETROL (Pr), Unik

Description.—Each 20-mg. tablet contains: methamphetamine HCl 5 mg., methamphetamine saccharate 5 mg., amphetamine sulphate 5 mg., dextro-amphetamine sulphate 5 mg.
Indications.—For appetite control in management of obesity.
Administration.—Initial dose, ½ tablet 3 times daily, increased if necessary to 1 tablet 2 or 3 times daily.
How supplied.—Bottles of 50 and 1000.

HÆMATINIC

Ferrous fumarate; PALARON, S. M. P.

Description.—Each flavoured, uncoated scored tablet contains: ferrous fumarate 200 mg., ascorbic acid 125 mg.
Indications.—Iron-deficiency anæmias.
Administration.—Adults, 1 or 2 daily as prescribed. Children, ½ tablet daily. May be chewed, dissolved in the mouth or swallowed whole without medicinal after-taste.
How supplied.—Bottles of 100 and 1000.

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MISCELLANY

OLD AGE

[The study of old age by the aged themselves has carried its own conviction—from the time of Cicero onwards. We feel therefore that there is something to learn from the following simple but discerning comments by Mr. Charles Adams of North Hatley, Quebec.

Himself an octogenarian, he has known life in active achievement, and now faces and overcomes by his direct observation the frustration which he so clearly recognizes as one of the most dreary burdens of the aged.]

THE FEELING most apparent in the aged is that of frustration. They want to do things and find it to be impossible; a gentle slope becomes a steep hill, a mile is found to be five miles, packages weigh more than they used to weigh, the suitcase that one picked up jauntily in one hand has now become too heavy to lift at all, and all the things that at one time were easy and simple have become hard to do or even impossible.

Then, of course, there is the matter of illness. There is always *some* ailment suffered by old people, and in a nursing home these ailments may vary: heart conditions, rheumatic and arthritic troubles, partial paralysis and nervous disorders, high blood pressure and complications of all these ailments. Then, old people forget so much of what is happening about them. Their memory of things that happened long ago, even in early childhood, is quite good and they will talk of youthful pranks and parties with a measure of enjoyment. But recent happenings are blurred and mixed-up both as to time and place, bringing an unhappiness hard to dispel.

In order to understand the problems of aged people one must spend some time with them, and in an effort towards that understanding, the writer spent some months in a nursing home. It seems as if women live much longer than men do, for in this place and in others, as I am told, there are more women than men at the present time. Here, there are seven women and only one man, although up to a few weeks ago there were two men for a long time. These invalids were all in their 'eighties and one at least was ninety-two.

One 85-year-old man who had been famous in the field of art was very feeble and for the most part very quiet. His gentle manner endeared him to everyone, and sometimes he would be quick to smile and laugh at something which was said that he appreciated. At the table he would pick up a fork or spoon as if it was something quite precious, almost as if he was caressing it. No doubt in his active days as a portrait painter, he handled his brushes with great feeling, perhaps, too, with respect. Anyway, his hands and fingers moved with precision and without haste.

Quite different was an elderly maiden lady of quiet and gentle manner. She was pious and of a sincere and abiding faith in God. She was, while rather feeble physically, mentally alert. This gentlewoman had, as I think, spent her life in the service of others and was beautifully unselfish. She was not lonely or in any way frustrated because she was always taking thought for the needs of others and, always patient and kind, spent a lot of her time visiting those in the house who were helpless. She needed no consolation from others. Her days were spent peacefully and she was content with life.

In contrast was a woman of advanced years—a mother with children, grandchildren and even great-grandchildren. While quite healthy physically, she was mentally disturbed with impaired memory for present happenings, though clear enough in the memory of the past long ago. Here was a person, because of uneasiness, for whom everything seemed to be all wrong; nothing was right, neither people nor surroundings. She responded to kindness, but required much attention. Both hearing and eyesight were impaired, which increased the difficulty of caring for her. Another woman over 92 years old was also very discontented—full of self-pity and needing constant attention and indeed demanding it too, inclined to be dictatorial and not satisfied with her lot.

Quite different from any of the above cases was a man, old, but not so far advanced in life as the others, whose ailment paralyzed him. He was very emaciated and was also unable to speak, but had a clear mind and good hearing. He was very patient, made no complaint and was grateful for the attention he was given, glad to have people talking in his presence or directly to him; he would show his understanding by a sort of smile and with his eyes, or by a slight movement of his hands. All he had need of was physical care and the presence of others.

These cases will serve to show that every aged person is, first of all, an individual with personal problems and memories, having in common only the feeling of frustration and loneliness. All that can be done to make their lives worth while is kindness and companionship. For the most part they are unable either in mind or body to occupy their time with work of any kind. Those who can look back on a useful and productive life bear their years of inactivity with the best grace and the most contented mind, from which one is tempted to moralize that the best preparation for a happy old age must have its beginning in the earlier years of active living. A life well spent in usefulness to others and an abiding faith in a wise Providence should ensure a peaceful and contented state of "being old".

Frustration, loneliness and ennui are the problems of old age. Each individual is different in one way or another. Kindness, companionship and a great and all-embracing understanding are all that one can give to ameliorate the sad lot of those who have become very old.

LETTERS TO THE EDITOR

THE ACTION OF FLUORIDES

To the Editor:

Now that fluoridation is receiving more attention, it would be desirable if doctors in fluoridated areas were to look for side effects from the taking of fluorine. In the past there have been no leads. No one knew what to look for and consequently no reports were forthcoming, but now when the door has been opened it is to be hoped that there will be many individual observations on this topic. The searching of medical history sheets for clues and recordings of *early* side effects of sodium fluoride are the necessary and important ones. Of these the effects from lowering of

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calcium blood levels come first—a tendency to bleed evidenced by unfavourable results from surgical operations, both major and minor; undiagnosed skin lesions; all those conditions arising from œdema in the tissues as a consequence of slow clotting time; deterioration of skin and appendages; the ever increasing nervous and mental diseases aggravated by lack of calcium; and many others which will develop with time.

One need not be a specialist to see how sodium fluoride lowers calcium blood levels. One need only remember that in acute sodium fluoride (or fluorine ion) poisoning, the poisonous factor is in the sudden loss of calcium in the blood which would eventually lead to convulsions and death. It must be remembered also that the only treatment for the poisoning is to neutralize and restore calcium to the blood. One may say that calcium is the very crux of the whole situation, and calcium levels must never be lowered.

In rebuttal, fluoridationists might point out that dosages are so small that they could hardly figure.

We do not know the proper fluoride doses, nor do we know what manifestations may come from the smallest doses. There are no recognized normal fluorine blood levels and there are no known daily requirements for fluorine.

Personally, I am convinced that dosage of fluorides is definitely in the microgram level, and that fluoridation dosage, based erroneously as it is on water levels instead of blood levels, is anywhere up to a thousand times too strong. Even at the microgram level I have found and reported in the *Canadian Medical Association Journal* (81: 954, 1959) cases showing side effects. Since that report, still further cases have come to my attention where skin and its appendages have been affected, and they all point to fluorine. Several of the patients are living in Brantford.

So here we have a topic of the most absorbing interest and importance, and we must pursue it to the very limit.

WILLIAM A. COSTAIN, M.B.
1567 Bathurst Street,
Toronto.

To the Editor:

Your correspondent Dr. G. L. Waldbott (*Canad. M. A. J.*, 82: 940, 1960) implies that adjustment of the mineral fluoride content of municipal water supplies, as presently practised in over 40 Canadian centres, can result in toxic effects.

In this regard, the testimony of the New Zealand Commission of Inquiry on Fluoridation of Public Water Supplies is of interest:

"In Wellington, Mr. Penlington (an opponent of fluoridation) expressed the opinion that 'no doctor qualified to diagnose incipient fluoride poisoning was available and that the people of Hastings were faced with a new man-made disease, incipient fluorine poisoning, which is outside the range of the ordinary medical practitioner though the allergist and specialist have pointed to it.' The last allusion is, no doubt, to the opinions of Dr. Waldbott and Dr. Spira."

The Commission report continues:

"We do not agree with the implication contained in Mr. Penlington's remarks that the local doctors were incapable of dealing with the possibility of fluoride poisoning. The President of the Hawke's Bay Division of the British Medical Association, Dr. McPherson, stated that on 22 March 1956 the following resolution was passed at a meeting of his division:

'That this meeting reaffirms that on the basis of the available scientific evidence, and from local medical experience, there are no grounds for believing that the artificial fluoridation of the Hastings municipal water supply produces any deleterious effects whatsoever on the human constitution.'

'Dr. McPherson was authorized by his association, at a meeting held on 15 November 1956, to say that 'none of the twelve doctors present at the meeting had seen any cases with symptoms suggesting fluoride poisoning.'

"We are satisfied [continued the Commission Report] that the local doctors had considered in a responsible manner the need to watch for any symptoms which could possibly be related to fluoride poisoning. The evidence shows clearly that they rejected the possibility that the fluoridated water at Hastings could produce any harmful effects on the health of the inhabitants."

After extensive study, the Commission concluded by recommending the widespread use of the fluoridation process for the purpose of achieving an urgently needed improvement in the present serious state of dental health.

A similar commission recently has been appointed in Ontario. It will be interesting, in due course, to study their conclusions.

D. C. T. BULLEN, D.M.D.
1325 McQuarrie St.,
Trail, B.C.

CASH DONATIONS TO HOSPITAL-BUILDING CAMPAIGNS BY STAFF PHYSICIANS

To the Editor:

I am writing this letter to bring to your attention a situation that has gradually become more serious in the past five years in Metropolitan Toronto. I refer to the practice of solicitation of staff physicians in Toronto hospitals for large sums of money, both on an immediate and a timed pledge, in support of expansion programs of hospital buildings.

This situation appears to affect both teaching and non-teaching suburban hospitals. It has developed on a background of marked hospital bed shortage in the Metropolitan area, and there can be no question that keen competition for hospital staff positions has also been a factor.

I have it on good authority that these cash donations range between $500 and $5000 per man in many instances. Although sums higher than $5000 have been mentioned, I am unable to confirm that this is true.

The reasons advanced in support of these large cash donations generally fall into three categories:

(a) The doctors involved make their living from the hospitals, and directly benefit financially from increased bed capacity.

(b) Doctors enjoy large incomes and can afford such donations.

(c) Doctors should be prepared to "lead the way" in campaign donations by "pace-setting pledges".

There are several faults in reasoning inherent in the above statements. Regarding statement (a), it

should be manifestly clear that the output of a hospital is medical care, in the same manner that the output of a symphony hall is good classical music, or the output of the law courts is justice. One does not note that musicians on the one hand, or the legal fraternity on the other, are called upon to make large cash donations to the institutions where they make their living.

As regards (b) and (c), while it is true that doctors are, at the present time, enjoying a good income and can be expected to be community leaders, these assumptions completely disregard the large sums of money that physicians everywhere are giving and have always given, to worth-while community projects, including churches, United Appeal campaigns, and service clubs. Other organizations such as the Cancer Society and the Red Cross Society, the Multiple Sclerosis Society, etc., enjoy cash donations from physicians, and often free services from these physicians.

It should be clearly stated by the Ontario Medical Association to boards of governors of various Metropolitan hospitals that doctors' obligations towards the hospitals at which they enjoy staff positions include the ensuring of a high standard of medical care in those hospitals, and the provision of free treatment to any and all indigent patients coming under their care in that hospital.

Doctors, on their part, should realize the gradual tendency on the part of hospital boards to make increasing demands upon their financial resources for hospital building money, as the search for such money becomes more and more difficult. They should also realize that their acquiescence in meeting the unfair demands placed upon them indicates their acceptance of the situation and the principle that they are indeed benefiting financially and should therefore expect to be taxed. This situation can be readily compared with the unfair taxation burden placed on the property owner to finance the enormous school building program, irrespective of the fact that many of the children requiring education live in apartments, leaving him, as the householder, to bear the brunt of the educational costs of these children.

In conclusion, Sir, I would like to recommend that the Ontario Medical Association consider this matter, and recommend to all members of the profession that all demands for large sums of money from staff physicians, on anything but a purely voluntary basis, be condemned as unethical. The profession has collectively disowned "fee-splitting" as it leads to direction of patients to doctors for a cash consideration. Let us not stand idly by and allow a similar principle to govern the conditions of appointments to a hospital staff.

H. M. WALLIS, M.D.

Toronto 15, Ont.

CLINICAL EXPERIENCE WITH BRETYLIUM TOSYLATE

To the Editor:

Might I ask you to publish a correction in the bibliography of the paper "Clinical experience with bretylium tosylate" (*Canad. M. A. J.*, 82: 877, 1960). This is in item 6 of the bibliography, which should have read as follows:

6. CORCORAN, A. C. *et al.*: *Circulation*, 19: 355, 1959.

This article contains a careful study of the behaviour of electrolytes when chlorothiazide is administered and offers a challenging concept of the mechanism whereby chlorothiazide may enhance the effect of ganglionic blocking agents.

It is as follows: Chlorothiazide produces oligæmia, which in turn evokes intensification of vasomotor tone. This increases the "fraction" of hypertension sustained by the vasomotor system, establishing a degree of neurogenic hypertension, which is susceptible to relief by ganglionic blocking drugs.

I regret the occurrence of this error, for which I take the entire responsibility.

J. A. LEWIS, M.D.,
Chief of Service—Medicine.

Westminster Hospital,
London, Ontario.

OBITUARIES

DR. JOSEPH M. ALLAIRE, 80, died May 10 at Joliette, Quebec. A graduate of Laval University in 1907, he is survived by six sons and two daughters.

DR. FRANCIS E. BOUDREAU, 79, died May 29 at Moncton, N.B. The first French doctor to graduate from Dalhousie University in 1906, he practised in Amherst, N.S., until 1926, when he went to Paris to study. He returned two years later and practised in Moncton as an eye, ear, nose and throat specialist.

He is survived by his widow, one daughter and two sons.

DR. ESTHER GORSEY HOLLENBERG, 45, died in Winnipeg on May 7 after a long illness. Born and educated in Winnipeg, she graduated in medicine in 1938. After an internship in St. Boniface and Grace hospitals, she practised in Winnipeg with her husband, Dr. Jacob Hollenberg. She was a member of Shaarey Zedek Synagogue and served on the board of education, the National Council of Jewish Women and Hadassah.

Her husband, two sons and a daughter survive her.

DR. ARTHUR LEONARD JACOBS, 56, of The Pas, Manitoba, died on May 13. After graduating in medicine in 1928 from the University of Manitoba, he practised briefly at Fort William, then at Churchill and The Pas.

He is survived by his widow and a daughter.

DR. JAMES O'NEILL, 43, died May 6 in Montreal. Born in St. Foy, Quebec, he graduated from Laval University in 1943. He served in military hospitals in England during World War II. A neurologist and psychiatrist, he practised in Sherbrooke and later in Montreal.

Surviving are his parents, his widow, one daughter and two sons.

DR. AIME PERRIER, 66, died May 22 in St. Jean, Quebec. He graduated from Laval University in 1921.

Surviving are his widow, six daughters and six sons.

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DR. STUART MASON ROSE, 73, died May 7 in hospital in Lethbridge. Born in Minnedosa, Man., he graduated from Manitoba Medical College in 1911. He practised in Manitoba and Saskatchewan for 20 years before going to Lethbridge and specializing in radiology.

Dr. Rose is survived by his widow.

DR. HARRY CARVER SWARTZLANDER, 71, of Calgary died May 14 in hospital. Born in Omaha, Neb., he graduated from Creighton University School of Medicine in 1912. Dr. Swartzlander practised in Calgary for many years, moved to Clearwater, Fla., on his retirement in 1954 and returned to Calgary in 1959.

Surviving are his widow, a son, Dr. F. C. Swartzlander, Calgary, and one daughter.

PROVINCIAL NEWS

BRITISH COLUMBIA

Mr. R. M. Strachan, M.L.A., leader of the C.C.F. party in British Columbia, in a recent speech, dwelt on the matter of health insurance, and declared his party's intention, if it came to power, to institute a plan of compulsory general medical care in B.C.

He regretted the opposition voiced by the medical profession in Saskatchewan and elsewhere and accused the profession as a whole of a reactionary attitude. He attacked too the insurance companies and others who wished to make profit out of human misery due to illness.

The following is a statement given to the press by the B.C. Division of the Canadian Medical Association:

"Mr. Strachan's reported comments contain nothing new, as his party has favoured this policy for some time. The attitude of the medical profession can only be finally ascertained when the government of the day puts forward some detailed plan. Mr. Strachan has not consulted us on the details of his scheme—but the medical profession in B.C. does reiterate that the direct provision of medical care by the government is not as satisfactory a procedure as painted. The socialization of an entire profession cannot be viewed lightly, and we are not anxious to have our services become a political issue. The doctors of B.C. will continue to work with and for any system of providing health care that provides for the improvement of standards and that is concerned with the quality of care. We do not favour the compulsory employment of the physician by the state."—E. C. McCoy, M.D., President, B.C. Division, Canadian Medical Association.

ALBERTA

The President-Elect of the Alberta Division of the Canadian Medical Association, Dr. E. F. Donald of Edmonton, accompanied by the President of the Council of the College of Physicians and Surgeons, Dr. J. R. Ibberson of Calgary, has recently visited some of the districts. Accompanying these officials have been Dr. G. Monckton, neurologist, who has spoken on the subject "Dizziness", and Dr. D. Cooper Johnston, orthopædic surgeon, who has discussed "Principles and pitfalls in the treatment of fractures". The final member of the group was Dr. W. Bramley-Moore, Secretary of the Alberta Division and Registrar of the College.

As a result of recent resignations, by-elections to Council will have to be held in two of the districts. Dr. J. D. Wallace of Wainwright has become Director of the Hospitals Division of the Department of Health, and Dr. J. B. T. Wood of High Prairie has become Director of Emergency Medical Care Services and a member of the staff of the Division of Treatment Services of the Department of Health.

At the recent session of the Alberta Legislature certain amendments were made in the Medical Profession Act. The first of these stipulates that all interns carrying out their compulsory internship year and all senior interns in residence will be required to be registered under the Capital's Medical Profession Act. This resulted from representation made to the College of Physicians and Surgeons by the Associated Hospitals of Alberta. The problem was that residents or interns who accompanied air ambulance trips could not properly be considered legally qualified practitioners. A further amendment was introduced to provide for use of suspended sentences in disciplinary problems. Provision was also made for the granting of a restrictive type of registration which, it is hoped, will assist in the rehabilitation of members of the profession who find themselves in difficulties, without taking away their means of livelihood.

Recently the city-owned Royal Alexandra Hospital in Edmonton became the fourth hospital in that city to adopt the use of a form in which the doctors certify that patients whom they send for emergency admission are in fact emergency cases. The form must be filled in within 12 hours of admission and must give reasons which justify the classification of a case as an emergency.

Alberta's Provincial Poison Control Service which was developed by co-operation between the Alberta hospitals and the Department of Public Health is now in full operation.

Though the service was only instituted on March 7, 1960, reports for the first quarter indicate that valid records have been received covering 336 cases of accidental poisoning which occurred in Alberta during January, February and March. Thus it appears that the Service will achieve its objectives: (1) to have facilities for treatment of poisoning readily available at all times to all people of the province; (2) to compile statistics which will aid in devising ways and means of preventing poisonings through education or by restricting the sale and distribution of proven toxic substances.

To ensure universal availability of help in cases of poisoning, there have been set up: (1) Poison Treatment Centres which are located in the emergency ward of each of the 102 active treatment hospitals in Alberta. Here there are: (a) a cardwheel file, which holds 2400 cards containing information on practically all of the household chemicals, drugs and pesticides in common use in Alberta; (b) drugs, equipment and instruments used in handling accidental poisonings; (c) a reference book—"Clinical Toxicology of Com-

mercial Products" (Home and Farm), by Gleason, Gosselin and Hodge. (2) Poison Information Centres in the Calgary General Hospital and the University Hospital, Edmonton. These are on a direct-line telephone whose number is in possession of every Poison Treatment Centre and every member of the medical and pharmaceutical professions in the area served. Information is on hand covering virtually all poisons which might be used in the province and expert medical advice is available on a 24-hour basis. W. B. PARSONS

QUEBEC

Dr. Milton G. Townsend of Montreal was re-elected president of the Industrial Medical Association of the Province of Quebec for a second term at the annual meeting held on May 26. Other members of the Board of Directors for 1960-61 are: Dr. H. Graham Ross, Montreal, honorary president; Dr. Raymond Caron and Dr. Donald Bews, Montreal, 1st and 2nd vice-presidents; Dr. Lloyd Birmingham, Montreal, secretary; Dr. Peter Vaughan, Montreal, treasurer; and Drs. Eustace Morin, Quebec, Andrew Visser, Montreal, Emile Beaulieu, Port Alfred, Harold S. Hooper, Grand'Mère, and Ernest Boyle, Montreal, directors.

NOVA SCOTIA

Dr. S. J. Shane of Halifax has been designated one of the Chest and Heart Association Travelling Scholars for Canada for the year 1960. Dr. Shane is associate professor of medicine at Dalhousie University, and director of the Cardiac Unit of the Victoria General Hospital, as well as medical director of the Tuberculosis Unit of the Halifax Health Centre. This is an exchange scholarship with the Canadian Tuberculosis Association and involves visiting a large number of medical centres in the United Kingdom, to observe the newer techniques in the diagnosis and management of cardiac and pulmonary diseases, as well as to compare notes with British workers as to the recent advances in these fields in Canada. Dr. Shane will probably also visit France and the Scandinavian countries.

PUBLIC HEALTH

SURVEILLANCE REPORTS OF EPIDEMIC OR UNUSUAL COMMUNICABLE DISEASES

PARALYTIC POLIOMYELITIS

During the week ending May 28, two cases (one delayed report) of paralytic poliomyelitis were reported to the Epidemiology Division. Six cases were reported the previous week. The 1960 cumulative total is now 102.

BACILLARY DYSENTERY

An outbreak of gastroenteritis has been reported at the Guy Indian Residential School in Manitoba, involving about 50 children and 10 adults. Four stool specimens were positive for *Shigella flexneri* II.

STREPTOCOCCAL SORE THROAT

About 40 cases of streptococcal sore throat, affecting children and adults, have been reported on the Indian Reservation at Nelson House, Man.

ROCKY MOUNTAIN SPOTTED FEVER

Further information has been received on the case of Rocky Mountain spotted fever, reported in the Surveillance Report of May 7, from Lethbridge, Alta. A wood tick was removed on April 19. The patient was admitted to hospital on April 21 complaining of headaches and pains on the left side. The temperature was 104° F.; the spleen was palpable and tender. A few scattered spots on the left wrist and hand appeared on April 23 and lasted for 48 hours. After treatment with tetracycline, 250 mg. q.6 h., the temperature became normal on April 22. The results of complement fixation tests are not yet available.

Indian and Northern Health Services

An influenza-like illness has been reported in a family of four at Foxe Main, N.W.T. A girl, aged 10, died 12-15 hours after the appearance of extreme cyanosis, dyspnœa and pulmonary œdema. Temperature varied between 99 and 102° F. It is expected that the infection will spread among the local Eskimo population. Viral studies are under way.

TRICHINOSIS

Four more cases of trichinosis have been reported in the Province of Quebec for the week ended May 28.

RABIES IN ANIMALS

Ontario.—Since January 1, 126 wild and 74 domestic animals were proved to have rabies, a 65% reduction as compared with the corresponding period of 1959. This is the lowest incidence of rabies in Ontario in the past five years. This marked reduction is attributed to the decrease of the disease in the fox in Southern Ontario. During the past three years the districts in Northern Ontario have been comparatively free of rabies. However, since the first of this year, the rabies cycle has again appeared in Temiskaming, Sudbury, Algoma and Parry Sound where foxes proven rabid have been found.

Although there has been a marked overall reduction in the reports of proven rabies in Southern Ontario, the reduction is based on the marked decrease (72%) in the number of cases of proven rabies reported in the fox. There has been no reduction in the number of skunks proved rabid during the current year. Skunks, therefore, constitute a grave local problem to the municipality. In 11 counties in Ontario, skunks proved rabid were the only wild creatures reported with rabies. Six of these counties reported proven rabies in cattle, dogs, cats and horses.

The continued appearance of skunk rabies in Southern Ontario poses a threat to man and animals. With the approach of summer, owners of dogs and cats should be warned to protect their animals and also to keep their pets from running at large. The skunk is more domesticated and frequently is seen in cities and towns. Parents should be warned of the danger of these animals to children. No person should handle these animals or treat them as pets. Skunks may be in the incubative stage of rabies when taken from their habitat.

Epidemiology Division, Department of
National Health and Welfare.

Ottawa, June 4, 1960.

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ABSTRACTS *from current literature*

MEDICINE

Serum Lipoproteins in Patients with Intermittent Claudication and with Myocardial Infarction.

P. J. NESTEL: *Circulation*, 21: 522, 1960.

The serum beta/alpha lipid ratios were estimated by electrophoresis in four groups of people. The study comprised 44 male patients with intermittent claudication; 61 men who were matched for age with the previous group and who were clinically free of cardiovascular disease; 30 male patients who had recently had a myocardial infarction; and a further group of 30 male controls whose physical activity was limited by factors other than disease.

The highest mean serum beta/alpha lipid ratio was found among the patients with intermittent claudication and was very significantly higher than the ratios found among the other three groups. The difference in the ratios between the patients with myocardial infarction and the two control groups was not significant. The importance of these findings is discussed. S. J. SHANE

Iodide-Induced Myxœdema.

J. T. TAGUCHI AND T. G. SKILLMAN: *Am. J. M. Sc.*, 239: 417, 1960.

Myxœdema resulting from administration of iodide to a euthyroid individual is a relatively rare occurrence, despite the widespread use of iodides and iodide-containing drugs.

The case of a 65-year-old man is presented in whom myxœdema resulted from prolonged iodide ingestion for chronic lung disease. Prompt recovery followed discontinuance of iodides and this relationship was clearly demonstrated when the entire clinical and laboratory picture of myxœdema was reproduced by re-administration of iodides. A review of the literature revealed 22 reported cases of this phenomenon.

The exact pathological physiology of this type of myxœdema remains obscure. However, it would appear most probable that high levels of iodide inhibit thyroid hormone synthesis by interfering with organic binding. The rare occurrence of this phenomenon would also suggest that this occurs in individuals whose thyroid glands are unusually susceptible to the inhibitory effects of iodide. S. J. SHANE

Serum Potassium and the Electrocardiogram in Hypokalæmia.

W. F. WEAVER AND H. B. BURCHELL: *Circulation*, 21: 505, 1960.

A definite correlation can be established between the electrocardiogram and the serum potassium level at hypokalæmia levels. A study was made at the Mayo Clinic of 130 hypokalæmic patients with relatively stable clinical states. Variations in Q-T intervals, P-R intervals, atrial rhythm, P waves, T/R values, and T-wave and U-wave contour in hypokalæmia were noted, as were the relationship between the T-U complex, electrical repolarization phenomena and potassium metabolism. Since modifying factors, such as drugs, certain electrolyte disturbances, variations in cardiac rate, conduction defects and myocardial ischæmia, were eliminated by careful selection of patients, only the influence of acid-base imbalance, sodium-potassium ratio, and hypertension on the electrocardiogram was studied. Acid-base imbalance and hypertension often simulated or obscured electrocardiographic evidence of hypokalæmia.

Electrocardiographic criteria in hypokalæmia include various combinations of the following signs: (1) T/U value of 1 or less in lead II or V_3, (2) U-wave amplitudes of greater than 0.5 mm. in lead II or greater than 1 mm. in V_3, and (3) S-T depression of 0.5 mm. or more in lead II or leads V_1, V_2 and V_3. It must be remembered that a normal electrocardiogram does not exclude hypokalæmia and that an electrocardiogram which fulfils the established criteria does not necessarily indicate hypokalæmia unless the factors discussed have been eliminated or minimized. S. J. SHANE

Heart Catheterization and Angiocardiographic Findings in Idiopathic Cardiac Hypertrophy with Endocardial Fibroelastosis.

J. LYNFIELD *et al.*: *Circulation*, 21: 386, 1960.

Of 32 patients with endocardial fibroelastosis, six were studied by means of clinical, roentgenological, electrocardiographic, and phonocardiographic examinations. Right heart catheterization in combination with left heart catheterization was performed in four, and two patients were studied by right heart catheterization alone. Angiocardiograms were performed in all six. The diagnosis was confirmed by autopsy in four of the six cases.

On the basis of the clinical, roentgenological, electrocardiographic, cardiac catheterization and angiocardiographic findings, the authors divide the patients into two types: Type I is characterized by a dilated left ventricle and signs of left ventricular enlargement and failure. Type II is characterized by a normal-sized or contracted left ventricular cavity and more prominent findings of pulmonary hypertension and right ventricular hypertrophy secondary to impaired left ventricular function. This classification agrees with well-known pathological classifications. The basic lesion appears to be a disturbance of myocardial function, the cause of which has not yet been determined. S. J. SHANE

Renal Involvement in Progressive Systemic Sclerosis (Scleroderma).

R. J. LEVINE AND B. R. BOSHELL: *Ann. Int. Med.*, 52: 517, 1960.

This paper demonstrates that renal disease is a not uncommon manifestation of progressive systemic sclerosis. Although this renal involvement may run a benign, protracted course, the more common and significant manifestation is acute renal failure, with relentlessly progressive oliguria and azotæmia, often associated with a malignant form of hypertension. In this situation a characteristic triad of lesions is observed in the kidney, consisting of intimal proliferation of the small intralobular arteries and arterioles, fibrinoid necrosis involving the walls of the afferent arterioles and sometimes the glomerular loops, and focal cortical infarctions. The course when this acute renal lesion becomes clinically manifest is unremittingly downhill. Currently available modes of therapy are not effective, and may even be harmful. Five illustrative cases are presented along with results of four necropsies. S. J. SHANE

(Continued on page 93)

NEWS & VIEWS
ON THE ECONOMICS OF MEDICINE

Prepared by the Department of Medical Economics. The Canadian Medical Association

NUMBER 8

Our sources of information are private communications and published comments in medical journals and the lay press. These are usually reliable but incorrect quotation or interpretation is always possible.

General Council met in Banff on June 13 and 14 to review C.M.A. activities of the past year and to make policy decisions for the future. Within the general area of medical economics there was much to discuss:

- the Special Committee on Prepaid Medical Care presented its initial report based upon the replies received from the Questionnaire on Health Insurance. Most of the data was informative and useful to Council in its subsequent deliberations. In a few instances, however, the validity of the Committee's conclusions was questioned. These were referred to the Executive Committee for re-checking.

- representatives of the Saskatchewan Division indicated to Council their continued opposition to the announced intent of the Government of the province to institute a compulsory, government-controlled plan of medical services insurance. Concern was expressed that Premier Douglas had chosen to regard the re-election of his party as a mandate to implement this program disregarding the fact that his substantial majority in seats was obtained by a minority (41%) of the popular vote.

- General Council, indicating support of the Saskatchewan Division passed the following resolution:

"The Canadian Medical Association believes that a single government-controlled scheme of medical care is not the answer to our health problems."

- General Council approved the action of the Executive Committee in proffering such financial and other assistance as the Saskatchewan Division required during the remainder of this calendar year.

General Council then proceeded to consider a Statement on Medical Services Insurance which the Committee on Economics had proposed after a two year study. In a preamble the Committee suggested to Council that a new statement should be promulgated specifically related to medical services. Previous statements, issued before the implementation of the hospital plans, referred to all elements of health care and were somewhat ambiguous in interpretation.

General Council approved the following statement first setting out the beliefs of the profession as to the proper role of governments and private enterprise in the provision of medical services insurance and then listing those principles which are the basic essentials of any medical services insurance program which the C.M.A. would actively support.

THE CANADIAN MEDICAL ASSOCIATION
STATEMENT ON MEDICAL SERVICES INSURANCE

The Canadian Medical Association believes that:

The highest standard of medical services should be available to every resident of Canada.

(over)

Insurance to prepay the costs of medical services should be available to all regardless of age, state of health or financial status.

Certain individuals require assistance to pay medical services insurance costs.

The efforts of organized medicine, governments and all other interested bodies should be coordinated towards these ends.

While there are certain aspects of medical services in which tax-supported programs are necessary, a tax-supported comprehensive program, compulsory for all, is neither necessary nor desirable.

* * * * * *

The Canadian Medical Association will support any program of medical services insurance which adheres to the following principles:

1. That all persons rendering services are legally qualified physicians and surgeons.
2. That every resident of Canada is free to select his doctor and that each doctor is free to choose his patients.
3. That the competence and ability of any doctor is determined only by professional self-government.
2. That within his competence, each physician has the privilege to treat his patients in and out of hospital.
5. That each individual physician is free to select the type and location of his practice.
6. That each patient has the right to have all information pertaining to his medical condition kept confidential except where the public interest is paramount.
7. That the duty of the physician to his individual patient takes precedence over his obligations to any medical services insurance program.
8. That every resident of Canada, whether a recipient or provider of services, has the right of recourse to the courts in all disputes.
9. That medical services insurance programs do not in any way preclude the private practice of medicine.
10. That medical research, undergraduate and postgraduate teaching are not inhibited by any medical services insurance program.
11. That the administration and finances of medical services insurance programs are completely separate from other programs, and that any board, commission or agency set up to administer any medical services insurance program has fiscal authority and autonomy.
12. That the composite opinion of the appropriate body of the medical profession is considered and the medical profession adequately represented on any board, commission or agency set up to plan, to establish policy or to direct administration for any medical services insurance program.
13. That members of the medical profession, as the providers of medical services, have the right to determine the method of their remuneration.
14. That the amount of remuneration is a matter for negotiation between the physician and his patient, or those acting on their behalf; and, that all medical services programs make provision for periodic or automatic changes in remuneration to reflect changes in economic conditions.

OTHER ACTIONS OF THE GENERAL COUNCIL

In addition to its extended consideration of the issues of prepaid medical care and the elaboration of a new statement of policy, the General Council –

- noted with regret the death of 106 members during the past year and approved the proposal to encourage the compilation of biographies of pioneer physicians.
- expressed its welcome to Dr. E. R. C. Walker, Scottish Secretary of the B.M.A., who with Mrs. Walker attended the Annual Meeting as guests of the Association.
- approved the projection of Annual Meetings up to and including the Centennial Meeting in 1967.
- noted the highest-ever membership of 13,978 in 1959.
- authorized affiliation with two additional national medical societies and, by resolution, expressed its support of the activities and methods of the fourteen national medico-lay organizations which are affiliated with the C.M.A.
- received the report of the completion of the addition to C.M.A. House.
- noted with regret the resignation of Dr. S. S. B. Gilder as Editor and welcomed his successor, Dr. Donald C. Graham.
- approved the efforts of the Executive Committee to achieve improvements in the Sick Mariners' Service and the Indian and Northern Health Services.
- congratulated the Special Committee on Prepaid Medical Care on its Questionnaire on Health Insurance and referred back for verification the replies to three sections.
- noted the participation of the C.M.A. with insurance and other national carrier organizations, in the formation of the Canadian Conference on Health Care.
- authorized the establishment of a Canadian Medical Non-Registered Savings Plan as a companion to the Canadian Medical Retirement Savings Plan.
- approved the acceptance of public funds for the support of the Canadian Council on Hospital Accreditation.
- endorsed the continued support of the British Commonwealth Medical Conference and instructed the C.M.A. representatives to the World Medical Association to support the cause of reform in the latter organization.
- expressed the pride of the profession in the expert aid rendered by Canadian physicians, physiotherapists and nurses in the disaster in Morocco.
- approved the participation of the C.M.A. in the organization of an Educational Secretariat to operate under the auspices of the Association of Canadian Medical Colleges.
- debated extensively and finally approved the suggestions made to the Royal College of Physicians and Surgeons of Canada for further recognition of certificated specialists.
- noted that the operating surplus of $84,000 achieved in 1959 was entirely due to publishing operations and received the prediction of the Honorary Treasurer that increased activities and consequent expense would likely require an increase in the membership fee.

- discussed the report of the Committee on Maternal Welfare and noted with approval the widespread activity of Divisional committees in investigating maternal deaths with a view to achieving a further reduction in mortality.
- approved the establishment of a complementary study of neonatal and infant mortality under the auspices of a new Committee on Child Health.
- expressed intense interest in the report of the Committee on Public Health and approved, on division, immunization of adults against poliomyelitis by public clinics and industrial groups as a supplement to the efforts of private practitioners; referred back for a more definitive statement the section on cigarettes and lung cancer and endorsed the mouth-to-mouth technique of resuscitation as "the most efficient and readily available method". Approved the studies of the Committee in relation to physical fitness as a concern of physicians and authorized cooperation with other agencies interested in promoting fitness.
- received with interest the report of the C.M.A. representatives on the Canadian Council on Hospital Accreditation.
- debated in detail the report of the Committee on Medical Education and referred it back for further study and more representative definition of a teaching unit.
- approved the recommendation of the Committee on Ethics for a restatement of the duty of physicians with respect to the dispensing of commodities.
- requested further study by the Committee on Nutrition of the decision of the Canadian Council on Nutrition that the addition of Vitamin C to evaporated milk should not be recommended; approved the Statement on Weight and Weight Reduction elaborated by the Committee.
- endorsed the report of the Committee on Rehabilitation including a Basis for Approval of Schools of Physical and/or Occupational Therapy in Canada.
- amended the report of the Committee on Pharmacy in respect to one observation on the safety and usefulness of iron-dextran compounds.
- congratulated the Committee on Medical Aspects of Traffic Accidents on a useful year's work, commended several Divisional committees for their pursuit of special projects and endorsed the recommendations of the Canadian Ophthalmological Society on visual standards for drivers.
- referred back the report of the Committee on Income Tax for wider consultation and further study.
- accepted the reports of the Committees on Approval of Schools for Radiological Technicians and Schools for Laboratory Technologists.
- debated exhaustively the report of the Committee on Public Relations and by a close vote referred to the Executive Committee a series of three supplementary recommendations involving sizeable expenditures for staff, consultants and peripheral facilities; noted with approval the record of a very active year in promoting the relations of the profession with the public.
- adjourned after marathon sessions involving two days and two evenings of meetings, with resolutions of thanks to the organizations and individuals whose arrangements made the discussions so productive.

(Continued from page 88)

SURGERY

Right-Sided or Segmental Ulcerative Colitis.

G. WATKINSON, H. THOMPSON AND J. C. GOLIGHER: *Brit. J. Surg.*, 47: 337, 1960.

Differentiation of segmental colitis, Crohn's regional colitis and other forms of ileocolitis from one another may be very difficult, but may be done pathologically. Crohn's disease is a granulomatous process involving all layers of the bowel wall, and ulcerative colitis is a diffuse ulceration of the mucosa with secondary inflammation of the other layers. Ulcerative colitis does not recur after colectomy, but Crohn's disease often does.

Segmental colitis appears to occur more often in women than men, and affects a younger age group in the second, third and fourth decades. Diarrhœa, often bloody, is the commonest symptom, and a palpable mass, usually in the right lower quadrant, the commonest sign. Manifest steatorrhœa is an indication of Crohn's disease. Both lesions show frequent perianal complications, and occasional stenosis or perforation. Arthritis may complicate segmental ulcerative colitis.

Medical treatment of this segmental colitis may result in long periods of remission, but the danger of a right-sided ulcerative colitis extending to involve the rectum and so make a permanent ileostomy necessary, is a real one, for a partial colectomy may be possible earlier without recurrence. On the other hand, surgical intervention in Crohn's disease or non-specific colitis may be regretted where recurrence is common.

Search must continue for a method of differentiating the varieties of segmental colitis so that treatment may be made more specific. BURNS PLEWES

Comments on Distribution of Blood Flow.

H. B. SHUMACKER, JR.: *Surgery*, 47: 1, 1960.

The reaction of the renal, portal, coronary and gastric circulation to various drugs, hypothermia, and shock is discussed, and comments are made on the possible therapeutic implications. Although these studies were carried out on dogs and are not yet complete, it is believed that they may be applicable to man. The reaction of the animals, even as with man, does not always appear to be a favourable or health-preserving one. Even moderate blood loss may sharply decrease renal blood flow as measured by direct methods. The use of vasopressors, which raise the pressure above a certain fixed point, tends to reduce significantly the blood flow to the kidneys. The dog's kidney seems able to tolerate a decrease in renal blood flow to 30% of normal for a 2½-hour period. Intravenous glucose and renal denervation tended to increase the blood flow to the kidney in these studies. The renal blood flow in shock may not correspond to the level of the systemic blood pressure. It is found that hypovolæmic animals at the same blood pressure level as normovolæmic animals may have only one-half the rate of renal blood flow. This may be due to a change in vascular resistance. The constant infusion of pituitrin intravenously may lower the portal venous flow and pressure, while at the same time the systemic arterial pressure increases. Although the cardiac output falls under hypothermia, the flow to the liver and kidneys is preserved in proportion at a level adequate for the reduced metabolic requirements.

The author mentions that in 1947, Ochsner and DeBakey advanced the idea of the borrowing-lending phenomenon (hemometakinesia). This means that if the effective blood volume remains the same and the cardiac output is unchanged, any increase or decrease in blood flow to a part of the body is possible only by a concomitant decrease or increase in flow to some other part. Reference to the original paper (*Ann. Surg.*, 126: 850, 1947) is advisable as it is not enlarged upon in this account. T. A. MCLENNAN

Open Operation in Treatment of Calcific Aortic Stenosis.

J. W. KIRKLIN AND H. T. MANKIN: *Circulation*, 21: 578, 1960.

Calcareous disease of the aortic valve, diagnosed by fairly uniform signs and measurements, was treated in 14 cases at the Mayo Clinic by an open surgical technique with utilization of extracorporeal circulation. One patient died during the operation and another died after leaving the hospital. Among seven patients followed up six to nine months after operation, definite symptomatic improvement was noted in six.

This disease is very dangerous, but a small improvement in the size of the valvular orifice can bring important benefits. The open operation is advantageous in that it avoids creating or aggravating insufficiency while relieving stenosis.

Presently this operation is advised for patients whose disability is significant or progressing. Severe co-existing coronary artery disease is a contraindication, but associated aortic valvular insufficiency, advanced degrees of disability, and left ventricular failure are not.

S. J. SHANE

Analysis of Death Following Cardiac Surgery.

J. L. HARRISON *et al.*: *J. Thorac. Cardiovasc. Surg.*, 39: 91, 1960.

In a review of 67 consecutive deaths following closed cardiac surgery, occurring over a five-year period, major groups consisting of patients with acquired valvular heart disease are compared.

The data suggest that cardiac asystole, the cause of the operating-room deaths, was associated with sudden or severe blood loss, definite periods of pre-arrest hypotension, increased myocardial irritability, and increased left ventricular end-diastolic pressure. The immediate postoperative deaths seemed predominantly related to post-surgical shock and to a lesser extent, frank congestive cardiac failure. The delayed postoperative deaths were almost invariably related to the presence of frank congestive heart failure. In most cases the shock and the congestive failure (not merely terminal events) were related to one or a combination of the following: (a) failure of the myocardium, despite good mechanical correction of the lesion, (b) aggravation of a pre-existing lesion, (c) production of a new lesion, and (d) failure to correct the mechanical lesion.

The exact place, in the above scheme, of other factors, such as digitalis toxicity, rheumatic activity, pericarditis, and myocardial dilatation or hypertrophy is limited by lack of knowledge pertinent to these phenomena. Far-advanced tissue damage and anatomical derangements of the valves themselves, of the myocardium and of the pulmonary vasculature, are, at present, major insurmountable obstacles in the practice of cardiac surgery. S. J. SHANE

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OBSTETRICS AND GYNÆCOLOGY

Indications for Therapeutic Abortion.

T. N. A. JEFFCOATE: *Brit. M. J.*, 1: 581, 1960.

Though the practice of therapeutic abortion varies widely in frequency from one hospital to another, the author's experience of 63 cases during ten years suggests that the need for the operation does not now arise more often than once in every 1000 pregnancies. Though the underlying principles governing a decision remain unchanged, the actual indications for terminating pregnancy alter rapidly with advancing medical knowledge. A relatively new indication is pulmonary insufficiency. Each case needs to be judged separately according to the special circumstances. Any one disease cannot be said to be always an indication for therapeutic abortion.

In making a decision the hazards of therapeutic abortion need to be weighed against those of the continuance of pregnancy. The gynæcologist who is expected to perform the operation should therefore always be one of those consulted before the procedure is suggested to the patient. The final decision rests with the patient and her husband.

Certain indications for therapeutic abortion are discussed, and it is noted that inherited traits and diseases such as rubella that threaten the health of the fetus are only acceptable legally when it can be shown that worry over potential fetal abnormality is adversely affecting the mother's health. Rhesus incompatibility can, however, be dangerous to the mother as well as to the fetus. Psychiatric indications are easily abused to justify the removal of an unwanted pregnancy.

Induction of abortion nowadays rarely offers hope of improvement or cure of the patient's disease; it generally aims to do no more than prevent deterioration of the mother's condition and is therefore more often prophylactic than therapeutic. ROSS MITCHELL

DERMATOLOGY

Present Status of Skin Tests.

C. J. C. BRITTON: *Practitioner*, 184: 427, 1960.

Skin testing is the most useful test we have in the investigation of allergic diseases. A positive skin test indicates the liberation of histamine or *H* substance at the site. Tests performed during or just after a severe attack of an allergic disease may fail to show a positive reaction, owing to exhaustion of the skin-sensitizing substance. The intensity of a specific skin reaction may be diminished by administration of antihistamines, ephedrine and other antispasmodics. Corticosteroids cause no significant change in the skin reaction. As a general rule it is wise to avoid administering medication for a period of 36 hours before testing. Skin tests may be positive in patients who are potentially sensitive even though they have not as yet shown any symptoms; 25% of apparently normal siblings of allergic children give positive skin reactions and those with a marked sensitivity develop hay fever for the first time several years later. The reason remains unexplained.

Negative skin reactions may also be found on rare occasions when testing patients who have a definite or even striking clinical sensitivity to an allergen. Here it must be remembered that we are testing the skin, whereas the shock tissue is the nasal or bronchial mucosa, so that false negatives can be expected. For these people the more delicate but unpleasant mucosal tests should be used.

Skin tests are of the greatest value in determining the responsible allergen. When the proper techniques are used, with potent standardized extracts, the correlation between history and skin tests is nearly perfect.

I. H. SHLESER

Incidence of Melanocytic Nævi in Young Adults.

O. C. STEGMAIER AND W. S. BECKER, JR.: *J. Invest. Dermat.*, 34: 125, 1960.

One thousand and ninety pigmented macular and papular lesions (excluding freckles) were removed from 20 volunteers between the ages of 20 and 25. Histological examination revealed that 815 were melanocytic nævi, 210 were lentigines and 65 were freckles or other non-nævi. An average of 40 nævi per person was found. Fifty per cent of the nævi exhibited epidermal-dermal junction proliferation.

ROBERT JACKSON

Pathogenesis of Silica Granulomas in Man: A Non-Allergic Colloidal Phenomenon.

W. B. SHELLEY AND H. J. HURLEY: *J. Invest. Dermat.*, 34: 107, 1960.

The essential features of a silica granuloma ("pseudotuberculoma silicoticum") are as follows: (1) appears at a site where foreign material containing silica is introduced, usually as a result of an injury, (2) appears as localized nodules after a completely asymptomatic latent period, the duration of which is measured in years, (3) appears histologically as an epithelioid granuloma, thus simulating tuberculosis or sarcoidosis. Silica occurs in all sorts of materials—from brick to talc, from dirt to kaolin. The latent period for development of granuloma averages ten years although a range from six months to 59 years has been reported. The presence of anisotropic crystals under polarizing light is the distinguishing histological feature. The authors made numerous intradermal injections into human volunteers of different types and concentrations of silica-containing materials. They found that in man silica in a non-colloidal form does not elicit an epithelioid granuloma. All forms of colloidal silica used in concentrations of 1/1000 or greater invariably produced an epithelioid response. The authors postulate that chemical weathering reduces the large silica-containing particles to the colloidal state in the skin. They found no evidence that the process of allergic sensitization was involved in any way.

ROBERT JACKSON

Postoperative (Pressure) Alopecia.

R. R. ABEL AND G. M. LEWIS: *A.M.A. Arch. Dermat.*, 81: 34, 1960.

Sudden loss of scalp hair was observed in eight women after operation. It followed long pelvic procedures utilizing the Trendelenburg position. A few days after operation five of the eight patients noticed œdema, exudation and crusting of the scalp on or near the vertex. One to four weeks later there appeared a patch of alopecia that resembled alopecia areata. Histopathologically, the distinctive feature was an obliterative vasculitis. Regrowth of hair occurred in from four to 12 weeks. The cause was considered to be pressure-induced ischæmia, resulting in temporary cessation of follicle activity. This theory was supported by experimentally produced alopecia in cats.

ROBERT JACKSON

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BOOK REVIEWS

METABOLIC HOMEOSTASIS. A Syllabus for Those Concerned with the Care of Patients. N. B. Talbot, R. H. Richie and J. D. Crawford. 132 pp. Illust. Harvard University Press, Cambridge, Mass.; S. J. Reginald Saunders and Company Limited, Toronto, 1959. $3.30.

This precious little book will be of value to the modern physician and surgeon who attempt to understand the dynamic metabolism of their patients and who attempt to maintain physiological conditions in the sick. It can be read quickly with much reward, and a copy should be obtained for handy reference.

It concerns the homœostatic systems for water, sodium, potassium, hydrogen ion, chloride and phosphorus. The first half of the book describes the limits of capacity of these body systems and their functional characteristics in health and disease. The second division of the syllabus illustrates by clinical experiences the manner in which such information can be used to improve and simplify patient care. A sensible number of references are given.

All data are in universal terms such as milliequivalents or milliosmols per square metre of body surface, or per kilogram of body weight, or per litre. It is pointed out that most body requirements, turnover rates and limits of tolerance are proportional to body surface area. Handy conversion graphs of all types are provided.

This book is excellent.

LA FATIGUE. PHYSIOLOGIE – PSYCHOLOGIE ET MEDECINE SOCIALE (Fatigue from the Physiological, Psychological and Social Medical Point of View). P. Bugard. 308 pp. Illust. Masson et Cie, Paris, France, 1960. $6.24 approx.

One cannot but be impressed, first of all, by the tremendous wealth of research material that has been brought together in this book and, secondly, by the accessible manner in which the information is laid out for the reader's inspection.

The book is manifestly the work of an endocrinologist, yet one with his feet very firmly on the ground, as he is able to discuss the widely differing aspects of the individual's response to his external and internal environments.

The problem of fatigue has been treated as involving the whole organism both psychically and physiologically, which indeed it does. We are taken through most exhaustive and complete descriptions of the psychological and organic factors involved, with physiological, biochemical and endocrinological explanations, which are complete texts in themselves. There is, to be sure, considerable repetition, mainly due to the method of detailing the fatigue of major activities such as sportsmen, industrial workers, directors, members of the armed forces in action, aircrew, those living in the tropics and the unfortunate deportés from France to Germany in the late war.

This book will undoubtedly become a textbook in the sense that it is very complete, down to an excellent bibliography at the end of each section. It is somewhat heavy going for the casual reader who wants to obtain a few facts, but everything faintly touching upon fatigue in its widest sense is carefully described and given due recognition.

It is published in a paper-back edition, and is certainly acceptable to the average reader. We should have more of this type of production.

THE HEALTH OF PEOPLE WHO WORK. Challenges of Occupational Health. Edited by A. Q. Maisel. 268 pp. The National Health Council, New York, 1960. $4.50.

This is an enlightening book for anyone interested in occupational medicine. It is not a catalogue of occupational diseases, but rather a concise record of the 1959 meeting of the National Health Forum of the U.S.A. At least a glimpse of the problems, goals, and challenges of the physician or nurse in various occupational programs is seen. Also, the principles or policies by which a modern occupational health program operates are outlined.

Part of the book deals with health services in small industries. Part-time nurses and doctors would possibly see a greater area for their services in health maintenance and health education. Opportunities for effective work in rehabilitation and placement are suggested. The importance of management understanding and their full co-operation is noted. A proper integration of the medical department into the business is necessary for achieving the ethical goals in industrial medicine.

There can be much ignorance among employees, management and physicians working in and outside industry about the role of the medical department. This book, which is not a text, helps to clarify the role and function of medical personnel. The reviewer believes that it can create a better understanding of the activities of industrial nurses and physicians and their opportunities to promote good health. It is obvious that this is possible through early detection of disease; timely referral for treatment, emergency treatment, periodic examinations, health education and counselling, and effective rehabilitation. Industry is increasingly aware of the greatest asset to any business, a healthy employee, and hence the interest in preventive medicine.

This book has a message for doctors, nurses and laymen in industry. Reading it should increase our awareness of the needs of industrial workers and our individual orientation to satisfy these needs.

BIOCHEMICAL ASPECTS OF NEUROLOGICAL DISORDERS. Edited by John N. Cumings and Michael Kremer, National Hospital, London, England. 230 pp. Illust. Charles C Thomas, Springfield, Illinois; The Ryerson Press, Toronto, 1960. $10.50.

This is a very handy little book valuable to anyone interested in the interweaving of clinical and biochemical investigations of disease and particularly useful for those concerned with neurological disorders. The book consists of 20 chapters, arranged in pairs, on the biochemical and clinical aspects of neurological disorders involving the B vitamins, demyelination, other aspects of lipid metabolism, porphyrins, calcium and phosphorus, copper, liver diseases and coma, anoxia and hypoglycæmia, the pituitary and adrenal glands, and muscle. The 19 authors are well known in their fields and each has written a brief, brisk summary of his subject.

The volume naturally has minor faults. This reviewer is a little irked to see, on p. 205, the ionic nature of quaternary ammonium substances incorrectly disguised. Figures for a "ratio of vitamin B to non-fat calories" are given, on pp. 13 and 17, without mention of the meaning or units involved in this strange term. The chapter on the biochemistry of disorders of lipid metabolism should have devoted at least a few phrases to description of the structures of

lecithin and the cephalins and of neuraminic and scialic acids. Readers who are expert in some of the subjects covered may complain of the occasional omission of other relevant points. The brevity of the volume is, however, perhaps its main virtue. The surveys of investigations and ideas are sufficient to give a clear picture of the present status of study and thought on all the disorders described. The bibliographies would provide a guide for those who need to go deeper.

Books such as this rapidly become out of date. This particular book should be a considerable help to research workers and thus contribute to its own outdating!

THE ROOTS OF CRIME. Selected Papers on Psycho-Analysis. Vol. II. Edward Glover. 422 pp. Imago Publishing Co. Ltd., London, England, 1960. $7.60 approx.

This book is a collection and fusion of work around the central theme of criminal behaviour which the author has previously published in sundry places. To use a book reviewer's cliché, and this time with emphasis, anyone who is interested in "crime" in any of its ramifications can hardly neglect reading it. It is written from a psychoanalytic viewpoint, by one of the most colourful of contemporary psychoanalysts, who manages without undue dilution of psychoanalytical concepts to make his subject matter understandable to any educated reader, at the same time that he and his discipline illuminate the subject. Especially is the book to be recommended to those whose work brings them into personal and professional contact with delinquents, psychopaths, prostitutes and homosexuals.

If any criticism is to be levelled at this volume, it probably is at the relative neglect of the role of unresolved depressive states as instigators of anti-social behaviour.

GENETIC BASIS OF MORPHOLOGICAL VARIATION. An Evaluation and Application of the Twin Study Method. Richard H. Osborne and Frances V. de George. 204 pp. Illust. Harvard University Press, Cambridge, Mass.; S. J. Reginald Saunders and Company Limited, Toronto, 1959. $5.50.

This attractive volume represents seven years of painstakingly collected and analyzed data amassed by the authors on certain morphological characteristics of 112 pairs of twins. Whatever else a reviewer may say about this ambitious, and, in some ways, pioneer undertaking, it should not be permitted to distract from the diligence of the investigators or from the value of their publication as a reference book.

In spite of some excellent discussions on such basic considerations as quantitative inheritance, and twin method of study, and some rather novel approaches to such concepts as body-build taxonomy and masculinity-femininity rating, this work is essentially a tabulation of data contained in 92 tables and four appendices. Table 77 is of particular interest, for herein are listed the 55 anthropometric measurements of the trunk, limbs, head and neck that were studied, and the relative importance of heredity, environment and sex in influencing these measurements is indicated.

The appropriate "ascertainment" of index cases has now come to be accepted as the keystone of any worthwhile investigation, for the validity of any "conclusion" is directly proportional to the appropriateness of the method of ascertainment. The authors are certainly conscious of this and do in fact enumerate most of the biases and pitfalls of the twin study method that must be avoided in obtaining a twin sample. In spite of this, and in spite of the lengthy explanations on why the sample was collected in the way that it was, the fact remains that in several important ways the sample is not representative of the twin population from which it was drawn. Furthermore, the ascertainment was unusual in that twins were not ascertained "blindly" through one member of the pair but through both members of each pair, i.e. twin pairs were ascertained and not individuals who are twins. Admittedly, and as the authors point out, the circumstances were also unusual, but one cannot help but wonder how reliable the conclusions are in interpreting the twin study method when data are collected in this way.

In many places the reviewer had difficulty in deciding when the authors were referring to the number of twin pairs and when to the number of individuals who are twins. That the authors understand this distinction must be accepted; nevertheless, on page 28 they give examples of "the relatively high frequency of congenital abnormalities in twins" which have been shown to be invalid because the distinction referred to above was not made.

The book is written mainly in the area of genetics and employs the highly specialized and often treacherous twin method of study. For this reason it cannot be recommended to the casual reader or to those who have not been initiated to the gene-environment complex.

FORTHCOMING MEETINGS

CANADA

PACIFIC DERMATOLOGICAL ASSOCIATION, Victoria, B.C., September 1-4. Dr. Edward J. Ringrose, Secretary-Treasurer, 2636 Telegraph Ave., Berkeley 4, Cal., U.S.A.

WORLD FEDERATION OF SOCIETIES OF ANÆSTHESIOLOGISTS, 2ND WORLD CONGRESS, Toronto, Ont., September 4-10. Dr. R. A. Gordon, Chairman of Organizing Committee, 178 St. George St., Toronto 5, Ont.

ONTARIO PUBLIC HEALTH ASSOCIATION, Toronto, Ont., October 3-5. Dr. G. K. Martin, Secretary-Treasurer, Room 405, 67 College St., Toronto, Ont.

CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Toronto, Ont., October 21 and 22. Dr. George H. Arronet, Secretary, Infertility Centre, Royal Victoria Hospital, Montreal, Que.

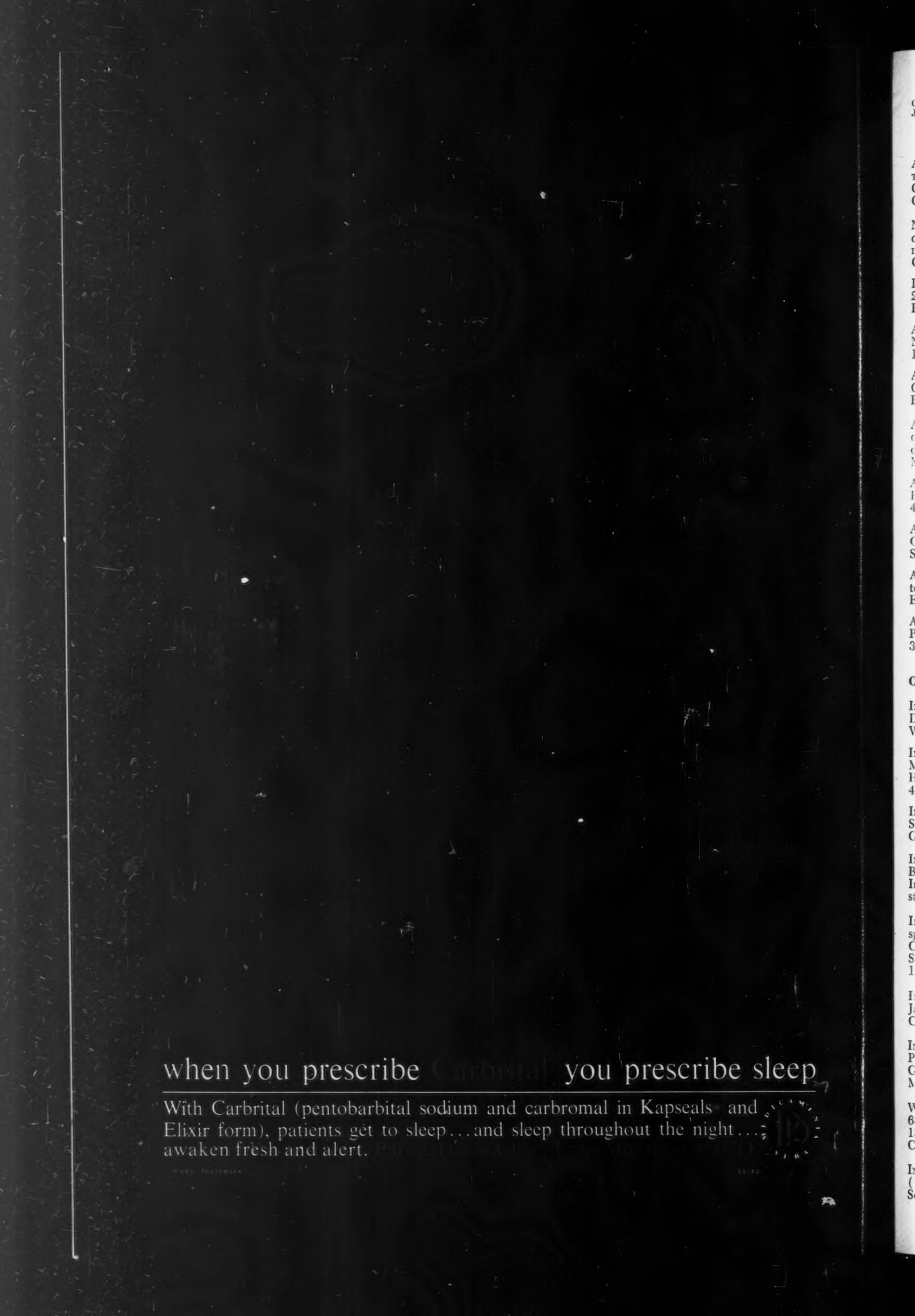
CANADIAN HEART ASSOCIATION AND NATIONAL HEART FOUNDATION OF CANADA, Toronto, Ont., November 30-December 3. Dr. John B. Armstrong, National Heart Foundation, 501 Yonge St., Toronto 5, Ont.

UNITED STATES

INTERNATIONAL CONGRESS ON OCCUPATIONAL HEALTH, New York, N.Y., July 25-29. Dr. Leo Wade, 15 West 51st St., New York 19, N.Y.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, Washington, D.C., August 21-26. Dr. W. J. Zeiter, 2020 East 93rd St., Cleveland, Ohio.

(Continued on advertising page 11)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With Carbrital (pentobarbital sodium and carbromal in Kapseals and Elixir form), patients get to sleep... and sleep throughout the night... awaken fresh and alert.

(Continued from page 97)

AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION, Washington, D.C., August 21-26. Mrs. Dorothea C. Augustin, Executive Secretary, 30 N. Michigan Ave., Chicago 2, Ill.

NATIONAL CANCER CONFERENCE, AMERICAN CANCER SOCIETY, INC., AND THE NATIONAL CANCER INSTITUTE, Minneapolis, Minn., September 13-15. Dr. Roald M. Grant, Coordinator, 521 West 57th St., New York 19, N.Y.

INTER-SOCIETY CYTOLOGY COUNCIL, Chicago, Ill., September 24-25. Dr. Paul A. Younge, Secretary-Treasurer, 1101 Beacon St., Brookline 46, Mass.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC., New York, N.Y., October 2-7. Mr. John W. Andes, Executive Secretary, 1 18 West Randolph St., Chicago 1, Ill.

AMERICAN PUBLIC HEALTH ASSOCIATION, San Francisco, Cal., October 31-November 4. Dr. Berwyn F. Mattison, Executive Director, 1790 Broadway, New York 19, N.Y.

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY, Chicago, Ill., October 9-14. Dr. William L. Benedict, Executive Secretary, 15 Second St. S.W., Rochester, Minn.

AMERICAN COLLEGE OF SURGEONS, Clinical Congress, San Francisco, Cal., October 10-14. Dr. William E. Adams, 40 East Erie St., Chicago 11, Ill.

ACADEMY OF PSYCHOSOMATIC MEDICINE, Philadelphia, Pa., October 13-15. Dr. Bertram B. Moss, 55 East Washington St., Chicago 2, Ill.

AMERICAN HEART ASSOCIATION, INC., St. Louis, Mo., October 21-25. Mr. Rome A. Betts, Executive Director, 44 East 23rd St., New York 10, N.Y.

AMERICAN COLLEGE OF GASTROENTEROLOGY, Philadelphia, Pa., October 23-26. Mr. Daniel Weiss, Executive Director, 33 West 60th St., New York 23, N.Y.

OTHER COUNTRIES

INTERNATIONAL CONGRESS OF ENDOCRINOLOGY, Copenhagen, Denmark, July 18-23. Dr. Henry H. Turner, 1200 N. Walker, Oklahoma City 3, Okla.

INTERNATIONAL CONFERENCE ON THE SCIENTIFIC STUDY OF MENTAL DEFICIENCY, London, England, July 24-29. Mr. Harvey A. Stevens, Chairman, 301 Troy Drive, Madison 4, Wis.

INTERNATIONAL CONGRESS ON ALCOHOLISM, Stockholm, Sweden, July 31-August 5. Dr. Archer Tongue, Secretary-General, Case Gare 49, Lausanne, Switzerland.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE (6th), Basle, Switzerland, August 24-27. The Secretariat, Sixth International Congress of Internal Medicine, Steinentorstrasse 13, Basle, Switzerland.

INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, sponsored by the Council on International Affairs, American College of Chest Physicians, Vienna, Austria, August 28-September 1. Mr. Murray Kornfeld, Executive Director, 112 East Chestnut St., Chicago 11, Ill.

INTERNATIONAL CONGRESS OF HÆMATOLOGY (8th), Tokyo, Japan, September 4-10. Organizing Committee, Science Council of Japan, Ueno Park, Taito-ku, Tokyo, Japan.

INTERNATIONAL CONGRESS OF PÆDIATRICS (10th), Lisbon, Portugal, September 9-15. Prof. Mario Cordeiro, Secretary-General, Clinica Pedietrica Universitaria-Hospital Santa Maria, Av. 28 de Maio, Lisbon, Portugal.

WORLD MEDICAL ASSOCIATION, 14th General Assembly and 63rd *Deutsche Arztetag*, West Berlin, Germany, September 17-22. Dr. Josef Stockhausen, Haedenkampstrasse 1, Cologne-Lindenthal, Germany.

INTERNATIONAL SYMPOSIUM OF CYBERNETIC MEDICINE (1st), Naples, Italy, October 2-4. Prof. Renato Vinciguerra, Secretary, Via Roma 348, Naples, Italy.

THE CANADIAN MEDICAL ASSOCIATION

JOURNAL

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

Editorial Office—150 St. George St., Toronto 5

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Bibliography *(13 clinical studies, 858 patients)*: **1.** Alexander, L. (35 patients): Chemotherapy of depression – Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Meprobamate and benactyzine hydrochloride (Deprol) as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy 6:648, Nov. 1959. **3.** Beerman, H. M. (44 patients): The treatment of depression with meprobamate and benactyzine hydrochloride. Western Med. 1:10, March 1960. **4.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. **5.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System 20:142, (Section Two), May 1959. **6.** Gordon, P. E. (50 patients): Deprol in the treatment of depression. Dis. Nerv. System 21:215, April 1960. **7.** Landman, M. E. (50 patients): Clinical trial of a new antidepressive agent. J. M. Soc. New Jersey. In press, 1960. **8.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression – New technics and therapy. Am. Pract. & Digest Treat. 10:1525, Sept. 1959. **9.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. **10.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. **11.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. **12.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy 7:28, Jan. 1960. **13.** Splitter, S. R. (84 patients): Treatment of the anxious patient in general practice. J. Clin. & Exper. Psychopath. In press, April-June 1960.

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MEDICAL NEWS *in brief*

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PHARMACEUTICAL INFORMATION BY TELEPHONE CALLS

A new method of supplying pharmaceutical information was inaugurated recently by Frank W. Horner Limited of Montreal. The project, known as Mediphone, is an exclusive telephone communication channel through which physicians may obtain various technical data on the use of Horner products. At present, 2000 English-speaking physicians in Eastern Canada may take advantage of this service on week days from 8.30 a.m. to 5 p.m. Eastern time. In off hours, a recording unit takes calls for action on the next working day. This system was conceived by Johnson and Lanman Inc., New York marketing agency, and utilizes the Bell Telephone Company's "long line system" for collect calls. It is possible that the Mediphone concept might interest other industries which have technical staff available to counsel customers by telephone on areas of product use, and are willing to share their experience on request. Depending on its acceptance by the medical profession, Mediphone may be extended nationally by October of this year.

CBC's FRONTIERS OF MEDICINE

This summer, between June 28 and September 6, CBC is presenting ten weekly programs dealing with medical research. The series, prepared by CBC's Outside Broadcast department in co-operation with the *Canadian Medical Association*, is entitled "Frontiers of Medicine". The programs are broadcast on Tuesday nights from 8:00 to 8:30 p.m. EDT on the Trans-Canada network.

In each program, three research centres are visited and the major part of the program consists of interviews with doctors and laboratory researchers across the country. There are also summaries of the advances in each field covered, past and present, and the outlook for the future.

Two programs have already been presented, one on Children's Diseases and the other on Diseases of the Eyes. A schedule of the future programs is as follows: July 12, Anæsthesia; July 19, Heart; July 26, Cancer; Aug. 2, Neurosurgery; Aug. 9, no program; Aug. 16, Mental disease; Aug. 23, Tuberculosis; Aug. 30, Arthritis; Sept. 6, Rehabilitation and geriatrics.

EMOTIONAL ASPECTS OF SCHOOL DESEGREGATION

A group of psychiatrists have attempted to explore some of the psychological bases for the strong personal involvement on the part of those who oppose desegregation (Emotional Aspects of School Desegregation (May 1960), by the Group for the Advancement of Psychiatry, New York). They point out that myths which have grown up about the Negro have depicted him as little better than a savage animal, intellectually and morally inferior, childish and irresponsible. (Nor are myths limited to beliefs about Negroes. For example, many people believe that all Scots are misers, all Englishmen stuffed

shirts, all Frenchmen lascivious.) In the case of the Negro, however, these myths serve to rationalize and justify the white person's disparaging attitudes, because he cannot clearly recognize and understand the real source of his prejudice. If we realize that myth-formation, psychologically, seeks to protect individual and group security against the sense of threat and to diminish anxiety, we can better understand why the myths of prejudice are so resistant to logic. The authors claim that in the United States white people have had to reconcile their belief in equality and Christian principles with their actual inhuman treatment of Negroes. In trying to solve this dilemma white people have created and defended various myths about the stereotyped Negro described above. Having created such myths, it becomes easier to justify their conduct, for principles of equality need not apply to so unworthy and inferior a group. Through a vicious circle these myths are nourished, sustained, and perpetuated. American Negroes as a group have in fact multiple handicaps — social, political, educational and economic — but these handicaps are a consequence of racial discrimination rather than of racial inferiority.

As a result of a myth that the Negro is sexually aggressive and virile, desegregation has been severely handicapped by widespread fears that the traditional barriers against sexual relationships between whites and Negroes will break down. Further, one of the prejudices learned in childhood is to believe that people of lower status groups are more primitive, aggressive, and potent sexually. According to the distortion of myths, the Negro male has great sexual prowess, and the Negro female is invariably responsive. This concept of the aggressive, primitive, potent Negro represents all that is bad and forbidden, all that the white adult, when reared to conform to middle-class social mores, has been denied. Unacknowledged white male jealousy of the Negro male's fantasied advantage as a sexual rival for the white female is an emotional source of power behind the extreme taboo, maintained by the white supremacy code, ostensibly to protect white womanhood. This code sanctions the most savage reprisals for Negro male violation. The irrational emotionality of a lynch mob reveals the terrible antisocial power of racial myths. The white-supremacy code also provides immunity to the white male from Negro resistance or retaliation for the white sexual freedom with Negro females.

As attitudes toward desegregation change, a series of stages can often be found. In the first stage, aptly described as walling off, a person gains new attitudes, but still retains some former ones, in spite of their contradiction. For example, a white parent may accept the fact that his child should attend a desegregated school, but will not permit a Negro child to visit his home after school. A later stage is reached when the white person denies that any differences exist between the two groups, despite the obviously different economic, social, and psychological conditions under which each lives. On a practical level this stage of attitudinal change carries

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with it the danger that special needs of certain children may go unheeded and unmet. Constructive acceptance of real differences is not the same as using these differences to justify disparagement or inferior treatment. Another stage is reached in the "mascot" attitude when white people in this stage overdo their admiration for the cuteness of the Negro child, for the Negro's gaiety, his gift for music, etc. They feel proud about having once invited a Negro to their home. This attitude still overlooks the real qualities of members of the other group, both positive and negative.

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LUNG BIOPSY IN DIFFUSE PULMONARY DISEASE

Because of the nature of their pathogenic development, diffuse lesions of the lung offer diagnostic difficulties. The interstitial areas and not the alveolar spaces are involved in the majority of disseminated diseases, with a resultant proliferative tissue reaction. As noted by Rich, the offending foreign material, whether bacterial or tumour, is distributed symmetrically through the vascular and lymphatic systems of the lung into the interstitial areas, without extension into the external communicating alveolar spaces. Unless material is excreted and discharged through the bronchial tree, the chance of identifying the pathological entity within the lung is slight by conventional means.

The very nature of disseminated disease excludes the possibility of extensive exudation throughout all areas of the lung, since there would not be enough functioning lung tissue to support life. Even when exudation is an accompaniment, the specific irritant or antigen can not be identified by the cellular exudate produced.

Scalene node biopsy is known to be a relatively simple technique and may be utilized on occasion to obtain tissue for diagnosis in patients with diffuse pulmonary disease. However, in the study of the value of nonpalpable scalene node biopsies, Shields and associates found that in patients with disseminated lung disease – exclusive of sarcoidosis – a positive diagnosis was established in only 20% by the scalene node biopsy. In patients with sarcoid, a positive biopsy was obtained in 80%, though when only diffuse pulmonary disease was noted without roentgenographic evidence of hilar node enlargement, the biopsy was frequently negative.

Direct lung biopsy would appear to be the best method of obtaining a diagnosis in patients with diffuse pulmonary disease. The technique favoured by Shields and Sweany (*Surg. Gynec. & Obst.*, 110: 585, 1960) is essentially that described by Klassen and associates in 1949, except that local anæsthesia with positive pressure breathing is preferred to general anæsthesia, with or without the use of an endotracheal tube; no postoperative chest drainage is necessary. They report the results of 36 biopsies in 35 patients. A definitive diagnosis was made in 31 of the 35 patients from the tissue obtained by lung biopsy. It was

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MEDICAL NEWS *in brief*

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nondiagnostic in three patients and wrong in one. In the 31 patients in whom a definitive lung biopsy was obtained, the tentative clinical diagnosis was confirmed in 55% of the patients, whereas it was found to be unsupported in 45% by final tissue diagnosis.

—

PERSPECTIVES IN THE TREATMENT OF DIABETES

Duncan, a highly respected leader in the field of diabetes, has emphasized that there is no substitute for diet therapy in the treatment of diabetes (*Am. J. M. Sc.*, 239: 397, 1960). Claims that more than one-half of the known diabetics in the U.S.A. are receiving the drug tolbutamide suggest, in his opinion, gross violation of this conservative truism.

More liberal quotas of protein and carbohydrate are indicated as a practical means of reducing the fat content of the diet. This seems to be especially desirable for the atherosclerotic patient with hypercholesterolæmia. Also, in these patients benefit accrues when the fat is provided in a high proportion of unsaturated forms.

Insulin in one form or another or in suitable combinations and by proper timing of administration is the most effective anti-diabetic agent known. Oral therapy is a treatment of convenience and not of necessity. The sulfonylureas are most effective, numerically, in those patients whose diabetes can be controlled without drug therapy. They have, however, a justified place in the management of approximately 10% of diabetic patients. They are effective supplements in the treatment of the overweight diabetic, but the likelihood that such effective agents might receive widespread adoption as a substitute for appropriate dietary measures must be guarded against. Failing in this would, and apparently does, mean that diabetes in this preponderant group of overweight subjects is not being as well treated, in the overall picture, as it was before these drugs were available.

Phenformin is a potent agent in lowering blood sugar and may prove to be of long-term value in the management of the juvenile type of diabetes. This has not yet been established. Phenformin is not considered a suitable substitute for sulfonylurea compounds in patients in whom they are satisfactorily effective. The optimum therapy for diabetes depends upon keeping diet, insulin and oral preparations in the proper perspective.

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SOUTHEASTERN STATES CANCER SEMINAR

The tenth Biennial Southeastern States Cancer Seminar for Physicians will be held at the Cherry Plaza Hotel, in Orlando, Florida, November 16-18, 1960. The theme "New horizons of cancer research and therapy" will be discussed by an outstanding faculty of 14 nationally prominent guest speakers.

This Seminar is being presented by the Orange County Medical Society in co-operation with the Florida Medical Association and supported jointly by the Florida State Board of Health and the American Cancer Society, Florida Division, Inc. There is no registration fee.

For advance reservations or further information, write: 1960 Cancer Seminar Committee, 17 Lake Street, Orlando, Florida.